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HIGH LIGATION OF THE INFERIOR MESENTERIC ARTERY DURING OPERATIONS FOR CARCINOMA OF THE DISTAL COLON AND RECTUM

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SUCCESSFUL LIGATION of the inferior mesenteric artery as a surgical procedure was first performed by Treves in 1898. In performing a resection of the colon for "idiopathic dilatation" he divided the left colic artery at the splenic flexure and the inferior mesenteric artery on the aorta. He then did a "pull-through" type of operation, bringing the splenic flexure through the anal canal, the patient making a good recovery. Kummel reported a case in which he successfully anastomosed the transverse colon to the rectum, having had to divide most of the branches of the inferior mesenteric above the last sigmoid artery. Hartmann advocated ligation of the inferior mesenteric artery as high as possible, not to facilitate a removal of a wider lymphatic field but to release the tension on the arteries of the sigmoid colon during the pull-through type of resection for carcinoma of the rectum. Jamieson and Dobson, in their classical article on the distribution of the lymphatics in the colon, advocated ligature of the vascular pedicle of the inferior mesenteric artery below the origin of the left colic artery. Moynihan (17) recommended ligature as high as possible on the inferior mesenteric artery, being confident that the marginal artery would be sufficient to supply the large bowel. Miles, in his description of excision of the rectum, ligatured the vessels at the level of the bifurcation of the aorta, i.e., probably below the first sigmoid artery.

During recent years, renewed interest has been aroused in the lymphatic spread of carcinoma of the distal colon and rectum. Grinell and Hiat reinvestigated the lymphatic drainage of the rectum and distal colon, confirming the distribution of lymph nodes along the inferior mesenteric artery and its branches, and they found that the incidence of lymphatic metastasis at the origin of the vessel was 17 per cent. They performed high ligation of the inferior mesenteric artery on the aorta in 41 cases—18

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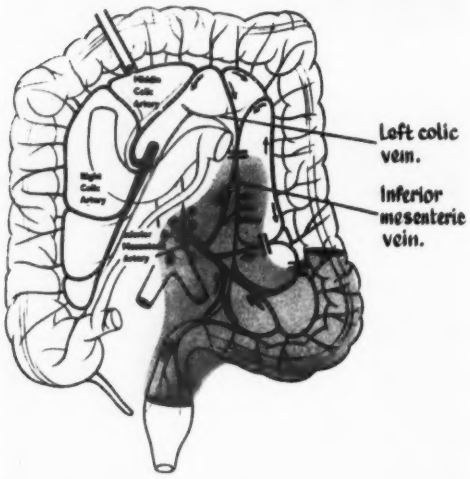

FIG. 1. Diagram showing the anatomy of the colic vessels. Note the site of election for a temporary transverse colostomy. The shaded area shows the extent of the mesentery resected during high ligation of the inferior mesenteric artery for carcinoma of the sigmoid colon or rectum. Arrows demonstrate the pathway of the lymphatic vessels, and circles, the distribution of the lymphatic glands along the arteries.

resections with anastomosis, 16 abdominoperineal resections, and 7 pull-through resections. Bacon and Smith, during operation, investigated the sigmoid artery in relationship to the operation of abdominoperineal proctosigmoidectomy. They were of the opinion that the inferior mesenteric artery should be ligated above the last sigmoid artery but did not advocate ligation of the artery on the aorta. When it is desirable to remove a wide lymphatic field in cases of carcinoma of the rectum, State has advocated the excision of the whole of the distal colon along with its mesentery, and ligation of the inferior mesenteric artery on the aorta with the construction of a terminal transverse colostomy. Ault, Castro, and Smith reported ligation of the inferior mesenteric artery at its origin in 12 cases of resection of the left colon. They were impressed by the adequacy of the blood supply to both the rectal stump and to the distal portion of the colon. Goligher reported a further 37 high ligations of the inferior mesenteric artery in cases of carcinoma of the distal colon and rectum. He stated that in 8 cases the blood supply to the terminal colon was inadequate, in 5 cases requiring immediate excision of additional colon. In 2 cases there was sloughing of the terminal colon which occurred following abdominoanal excision.

In the past there has been little difference in the 5 year survival rates following resection for carcinoma of the right as compared with the left portion of the colon. It would appear impossible to improve the results of surgical treatment for carcinoma of the right portion of the colon since the widest possible removal of the lymphatic field has been standard surgical practice for growths in this region. Removal of the lymphatic field in operations on the left portion of the colon has been more restricted because of the hazards of infection and inadequate blood supply. Advances in surgical technique and the advent of chemotherapy have made resection of the large intestine a less hazardous procedure, and more attention has been directed to wider radical resection for carcinoma of the colon, with particular reference to a greater clearance of the lymphatic field. Jamieson and Dobson demonstrated that the lymphatic drainage of the colon follows very closely the main blood supply. The lymphatic drainage of the rectum and descending colon, up to and including the splenic flexure, is along the main colic arteries to the aortic and inferior mesenteric group of glands, as shown by Jamieson and Dobson. We have also made this observation by injection of small quantities of sky-blue with hyalase into the submucosa of the colon at operation. The dye, being picked up very quickly by the lymphatics, passes on to the lymphatic glands draining the area, which are then dyed blue, thus illustrating the lymphatic drainage of the area involved. Jamieson and Dobson stated that, in their opinion, the main lymphatic drainage was to the para-aortic glands and not to the glands around the origin of the inferior mes-

enteric artery. Observations made at operation, and confirmed by histologic examination of the specimens, do not agree with their findings. It has been clearly demonstrated that the primary drainage of the rectum and colon is along the whole extent of the inferior mesenteric artery, and thence to the para-aortic lymphatic glands. In the descending colon the lymphatic spread extends along the paracolic glands, both upward toward the splenic flexure and downward to the sigmoid colon (Fig. 1). At the splenic flexure there exists a lymphatic water-shed, depending on the exact topography of the vascular supply. Jamieson and Dobson showed that some lymphatics from this region pass with the left colic vein to join the para-aortic glands, lying on the superior border of the pancreas, and others to the group at the origin of the middle colic artery.

In carcinoma of the rectum, Dukes (quoted by Morgan 1957) has shown that downward lymphatic spread is very rare and, for practical purposes, can be taken as occurring mainly in advanced cases and those of high grade malignancy with a poor prognosis. Upward lymphatic spread, however, is the most common route, and it would therefore appear necessary for radical removal of the left portion of the colon and rectum for carcinoma, to ligate the inferior mesenteric artery at its origin on the aorta, and thus to ablate the greatest possible lymphatic field.

It has been confirmed (6) that the adequacy of the blood supply to the distal colon is dependent on the marginal artery. In the absence of arterial disease, following ligation of the inferior mesenteric artery, the entire colon and rectum may be vascularized from branches of the superior mesenteric artery via the marginal artery. It is therefore anatomically permissible, during operative procedures, to ligate either the inferior mesenteric artery at its origin or its main branches before they join the marginal artery. This step enables a wide lymphatic field to be removed.

FIG. 2. Roentgenogram of injected autopsy specimen showing the commonest distribution of the inferior mesenteric artery. Note the left colic artery proceeding to the splenic flexure, and the bifurcation of the first sigmoid artery before it joins the marginal artery.

SURGICAL ANATOMY OF THE INFERIOR MESENTERIC ARTERY

Certain anatomic features of the inferior mesenteric artery and vein require careful attention during surgical procedures on the distal colon and rectum.

Ligation of the inferior mesenteric artery on the aorta necessitates dissection of the artery at its origin. For this, adequate exposure is essential, and the abdominal incision at operation must be adequate. The duodenum may require retraction upward as its third part is closely related to the origin of the inferior mesenteric artery. In some cases, this origin lies under cover of the pancreas; in these cases, high ligation of the inferior mesenteric artery at its origin is unjustifiable, being an unnecessarily hazardous procedure. No case of absence of the inferior mesenteric artery has been seen in either operative or autopsy specimens, although 1 such case was reported by Quain.

FIG. 3. Roentgenogram of an autopsy specimen showing the distribution of the inferior mesenteric artery. The first sigmoid artery is arising from the left colic artery. (This occurs in 30 per cent of specimens examined.)

There has been some confusion regarding the surgical anatomy of the blood supply to the left portion of the colon and the rectum, and investigation of the topography of the inferior mesenteric artery has been carried out by dissection of 100 cadavers (6).

A number of anomalies have been reported in the literature in connection with the branches of the inferior mesenteric artery. An accessory hepatic artery was seen to arise from the inferior mesenteric artery by Cavasse. Vicq D'Azyr noted the absence of a connection between the middle and left colic arteries. A further anomaly, not previously recorded, was encountered in the present investigation in 2 autopsies. The right and middle colic arteries were absent, and the whole colon was supplied by the inferior mesenteric artery which anastomosed with the ileocecal branch of the superior mesenteric artery through the marginal artery.

THE LEFT COLIC ARTERY

In 89 of 100 dissections, the left colic artery proceeded immediately upward and to the left toward the splenic flexure, and not to the descending colon, as illustrated in most textbooks and surgical articles. Proceeding upward it made an acute angle with the parent trunk of the inferior mesenteric artery and was crossed by the inferior mesenteric vein. At this point, both vein and artery are in close proximity to the left ureter, and when the vessels are ligated, care must be taken not to damage this structure. It has been noted that the left colic artery bifurcates near the splenic flexure and further that the marginal artery in this region is poor (Fig. 6). It is therefore important to preserve this bifurcation in all cases of high ligation of the inferior mesenteric artery, to enable an adequate blood flow from the branches of the superior mesenteric artery, to supply the marginal artery of the descending colon, and thus the whole of the left part of the colon. The left colic artery is absent in 6 per cent and in 5 per cent passes directly outward to the descending colon. When this occurs the marginal artery at the splenic flexure is well developed, and the left branches of the middle colic usually come well over toward the splenic flexure.

SIGMOID ARTERIES

The exact topography and distribution of the sigmoid arteries are not important. In most cases it is possible to see the sigmoid vessels clearly, and ligation can be carried out safely without damage to the marginal artery. Visual ligation of the sigmoid vessels is not always possible, especially when the mesosigmoid is loaded with fat, as in obese patients. In these cases the mesosigmoid must be divided far enough away from the mesenteric border of the colon to ensure that the marginal artery is undamaged. There is a tendency for the marginal artery to arch away from the colon at the point at which the sigmoid vessel joins it (Fig. 3), and if the sigmoid artery is divided too close to the mesenteric border, the marginal artery may be endangered at this point.

The first sigmoid sometimes bifurcates near the marginal artery. In such instances, if part of the sigmoid colon distal to the first

sigmoid artery is being retained to form either a colostomy or an anastomosis, it is expedient to preserve this bifurcation as a secondary arcade.

The anastomosis between the last sigmoid and the superior rectal arteries has been shown to be adequate by means of the marginal artery, or by the rectosigmoid arteries, as described by Pope and Judd and Griffiths (6) (Fig. 7). There is thus no contradiction to the division of the inferior mesenteric artery below the last sigmoid artery if this procedure is of any surgical advantage. It is important, however, to make quite sure that the marginal and rectosigmoid vessels are not damaged during mobilization of the lower sigmoid colon and rectum. The damage caused to the colonic vasa recta and to the rectosigmoid arteries during mobilization of the rectum and the tension exerted on those vessels by the operative technique occasioned much concern to surgeons in the early part of this century, since gangrene of the sigmoid colon and rectum during perineal or sacral pull-through resections not infrequently followed.

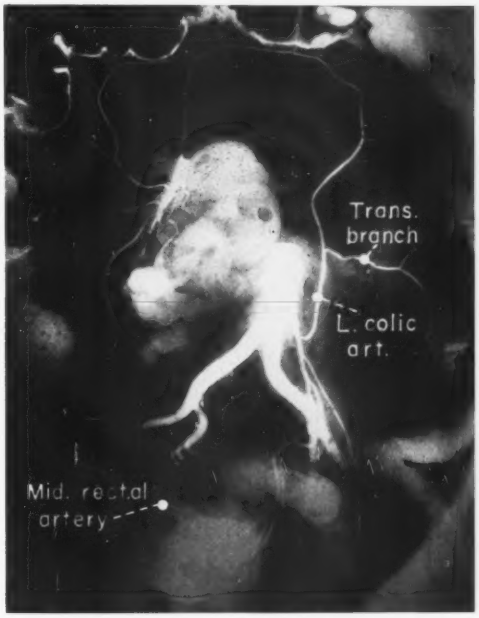

FIG. 4. Roentgenogram of injected autopsy specimen showing the transverse branch of the left colic artery which was seen in 25 per cent of autopsy dissections, and the middle rectal branches of the internal iliac artery.

THE MARGINAL ARTERY

Preservation of the marginal artery and its accurate ligature in relation to the site of division of the colon are of paramount importance. This vessel lies 1 to 1½ inches from the medial border of the colon and in obese patients is very difficult to identify. Its presence as a vessel running parallel to the colon is constant in the fixed portion of the colon on the left side. In the transverse colon, this vessel is formed by the large arcades of the middle colic artery, and, though it is usually present in the sigmoid colon, the first and maybe the second sigmoid artery when they divide near the bowel may partake to a great extent in its formation. The marginal artery may be damaged during mobilization of the colon, especially mobilization of the splenic flexure.

When a loop colostomy is constructed as an emergency procedure, care must be taken to place the colostomy rod through the mesentery near the bowel on the intestinal side of the marginal artery. This procedure prevents tension upon, and therefore damage to, the artery. A temporary transverse colostomy should be placed well to the right of the midline, to avoid damage to the left branch of the middle colic artery, since damage to the marginal artery at the site of the colostomy may well interfere with the anastomosis between the superior and inferior mesenteric arteries, and therefore contraindicate high ligation of the inferior mesenteric artery at subsequent operation on the left portion of the colon. If, however, there is an adequate branch of the middle colic artery to the left of the colostomy, then the "anastomotica magna" of Van Haller, i.e., the anastomosis between the middle colic and left colic arteries, will be adequate to supply the colon following ligature of the inferior mesenteric artery at its origin.

The vasa recta (or long arteries) of the colon arising from the marginal artery must

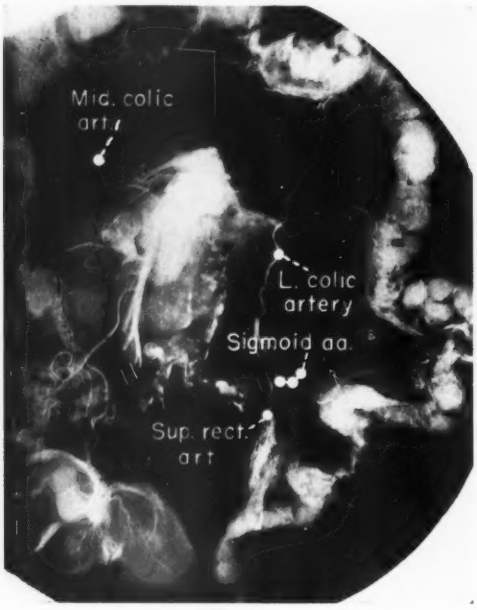

FIG. 5.

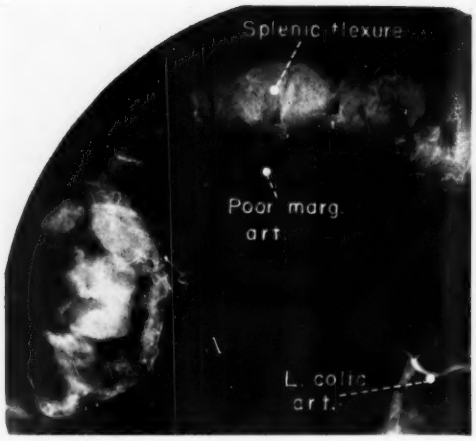

FIG. 6.

FIG. 5. Roentgenogram of injected autopsy specimen. Note the left colic artery and its bifurcation at the splenic flexure.

FIG. 6. Roentgenogram of an autopsy specimen showing the bifurcation of the left colic artery at the splenic flexure. Note the poor marginal artery at the splenic flexure.

never be divided, for the reason that there is very little anastomosis between these small vessels.

Ischemia may occur at the site of proximal division of the gut by ligature of the marginal artery too far above this point. There is no well marked anastomosis between the vasa recta, and the intramural plexus is not sufficient to develop an adequate collateral circulation. The freed colon may be held by an assistant so that the place where the marginal artery should be ligated may be gauged precisely. It is further suggested, in order to eliminate the danger of ischemia, that the marginal artery be divided about 1 inch *distal* to the site at which the colon is going to be divided.

The middle colic artery is absent in 22 per cent of cases, and its presence in the proximal transverse mesocolon should be verified, if possible, before ligation of the inferior mesenteric artery is performed. A large right colic artery, however, is sufficient for the maintenance of the blood supply to the distal portion of the colon in this circumstance.

MIDDLE RECTAL ARTERY

The middle rectal artery is capable of supplying the rectum, sigmoid colon and, in all probability, most of the descending colon, following ligation of the inferior mesenteric artery. It is upon the middle rectal artery that the viability of the distal segment of the colon or rectum, following resection, depends. This artery usually arises from the internal iliac as a number of branches, running in association with the vesical and vaginal or prostatic arteries, along the "lateral ligaments" of the rectum. It is therefore important that the rectum is not mobilized too far downward in the pelvis, especially laterally, during anterior resection of the rectum. It is true that, if the middle rectal arteries have to be divided completely during restorative resection of the rectum, a safer operation in such a case would probably be excision of the rectum with a terminal colostomy. When the rectum has to be totally mobilized down to the pelvic floor, the middle rectal arteries are divided, and the distal segment of the rectum is dependent on the relatively insignifican

inferior hemorrhoidal artery. This vessel is a somatic artery rather than a visceral vessel, and, although an anastomosis does occur in the region of the anal canal with the other rectal arteries, it is not particularly well developed and sometimes may not be sufficient to maintain complete viability of the rectal stump.

In operations performed for carcinoma of the descending colon (reported later in this article), in which high ligation of the inferior mesenteric artery had been carried out, the blood supply to the sigmoid colon, which was dependent upon the middle rectal arteries, was shown to be adequate in all cases.

It has been shown, both anatomically and experimentally, that the distal portion of the colon has an adequate arterial collateral circulation following the ligation of the inferior mesenteric artery at its origin. This procedure has been carried out in 220 surgical operations on the distal segment of the large intestine with only 1 death. This death may have been referable to high ligation of the inferior mesenteric artery causing vascular necrosis at the anastomosis, or possibly to ill-judged division of the marginal artery.

The indication for high ligation exists in any fit patient who has an operable and curable carcinoma occurring in the large intestine below the distal third of the transverse colon.

Contraindication to high ligation of the inferior mesenteric artery exists in the following cases: (1) the presence of extensive arterial disease, with evidence of cardiac involvement (hypertension alone is not a contraindication); (2) an ill patient in whom any added surgical procedure may be hazardous; (3) an obese patient in whom the colonic mesentery is fat laden, making identification of the exact vascular arrangements impossible (the added operative morbidity in these patients outweighs any beneficial result this procedure might produce); (4) incurable malignant disease secondary deposits in the liver or intraperitoneal spread that cannot be removed at operation; (5) a technically difficult operation in which any added risk would be unjustifiable.

FIG. 7. Roentgenogram of injected autopsy specimen showing the anastomosis between the last sigmoid and superior rectal artery.

OPERATIVE TECHNIQUE OF HIGH LIGATION OF THE INFERIOR MESENTERIC ARTERY

An adequate incision to ensure a good exposure is necessary if the inferior mesenteric artery is to be ligated at its origin. The left ureter should first be identified by making a peritoneal incision on the lateral side of the intersigmoid notch, and then passing a finger upward along the ureter to separate it from the peritoneum covering its anterior surface. This maneuver will prevent the ureter from being drawn up with the peritoneum during the dissection of the inferior mesenteric and left colic arteries; and, therefore, it is less likely to be accidentally damaged. Ligation of the vascular pedicle should be carried out early in the operation, as advocated by Cole, to prevent possible blood-borne metastasis from being produced during mobilization and handling of the neoplasm. As a preliminary procedure it may be wise to ligate the vascular pedicle in continuity at the level

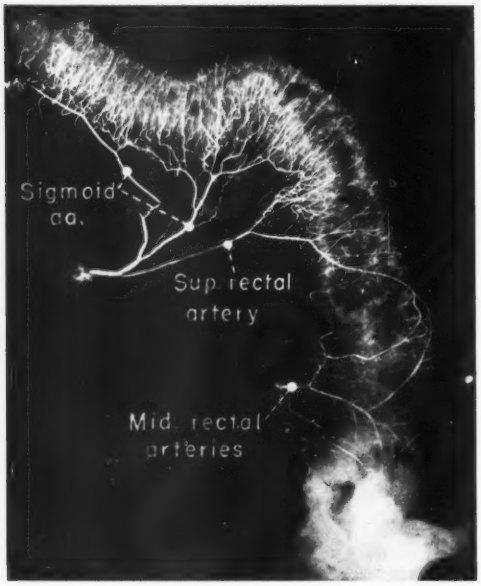

FIG. 8. Roentgenogram of an injected postoperative specimen following an excision of the rectum, high ligation of the inferior mesenteric artery having been performed. Note the middle rectal artery and its anastomosis with the superior rectal artery.

of the aortic bifurcation *before* any mobilization of the colon or rectum is undertaken.

To approach the origin of the inferior mesenteric artery, an incision is made in the peritoneum over the bifurcation of the aorta. A finger is passed under the inferior mesenteric artery, and the incision is extended upward along the right side of the abdominal aorta toward the duodenum. By holding the mesenteric vascular pedicle forward, the para-aortic tissue, including the para-aortic lymph glands, is dissected off the aorta. In so doing, it is necessary to divide the hypogastric sympathetic plexus. The duodenum is then retracted upward and the origin of the artery is defined. The inferior mesenteric artery is then divided and ligatured at its origin, leaving a sufficient stump to ensure a safe ligature.

The dissection of the peritoneum and para-aortic tissue is then continued laterally and upward toward the inferior mesenteric vein.

The inferior mesenteric vein is easily seen through the peritoneum, and since the left colic artery is in close relation to it the vein is a good guide to this vessel. These vessels are then ligatured together proximal to the bifurcation of the left colic artery, in close proximity to the duodenojejunal flexure. The incision is continued outward to the marginal artery, which must be identified, and then downward parallel to this vessel to the point selected for the division of the colon. If the site of the division of the colon is below the first sigmoid artery, it is advisable to save the bifurcation of this vessel if it is placed near the colon. As has been stressed previously, the marginal should be divided below the site of the division of the colon to ensure that no distortion of the vasa recta has been produced. The procedure of resection of the intestine, with the establishment of a left iliac colostomy or an anastomosis, is then carried out.

High ligation and removal of the whole lymphatic field in the presence of carcinoma at the splenic flexure or in the descending colon are imperative since the lesion lies nearer the inferior mesenteric vascular pedicle than more distally placed lesions.

The anatomy of the branches of the inferior mesenteric artery should be verified, but it is the viability of the bowel remaining after resection that must be determined for certain. Pulsation in the marginal artery is often difficult to see or feel and is therefore not a good guide to the adequacy of colic vascularization. In fact pulsation of even large vessels may be markedly diminished because of spasm from handling. A better indication is the color of the intestine, but the adequacy of blood supply is really proved by division of the marginal artery just below the site elected for a terminal colostomy or anastomosis before the application of an artery forceps. When the blood supply is poor, or in doubt, it will be necessary to mobilize the colon further until viable intestine is obtained; mobilization of the splenic flexure and transverse colon is often necessary.

PERSONAL SERIES (C. N. M.) OF 220 HIGH LIGATIONS

High ligation of the inferior mesenteric artery has been carried out in 220 cases; 214 were resections for carcinoma of the distal colon or rectum, and 6 for benign conditions of the colon, mistaken at operation for carcinoma, but later proved to be innocent. Four were cases of diverticulitis of the sigmoid colon, 1 a benign adenoma of the colon, and 1 a case of endometriosis of the rectosigmoid colon. Restorative resections were performed in all cases.

In the whole of this series, there was only 1 postoperative death which could have been attributed to devascularization of the colon. One other death occurred in this series which was due to an unrelated postoperative complication. A temporary fecal fistula, following an anterior resection, occurred in 1 case; this healed spontaneously in a few days. This may have been due to mechanical distention of the anastomosis, since the colon was loaded with feces because of inadequate preparation. In 1 case necrosis of a left iliac colostomy occurred, necessitating its reconstruction 3 days postoperatively.

A further analysis of this series into a pathologic classification will show that there is a possible advantage to be gained in this procedure (Table I).

Most surgeons will agree that high ligation of the inferior mesenteric vessels should enable a more radical operation to be undertaken.

Before high ligation of the inferior mesenteric vessels was practiced, the incidence of C_2 cases (a malignant gland present immediately below the site of ligature), was 16 per cent in 206 cases of carcinoma of the rectum and rectosigmoid. Since its adoption in suitable subjects, the incidence has been 13.8 per cent in 329 comparable cases. However, high ligation was carried out in only 162 cases of this latter group, therefore, the incidence of C_2 cases was actually only 8 per cent.

These figures suggest that the routine use of high ligation in suitable patients may result in the conversion of approximately 1 in 8 C_2 cases into C_1 cases (i.e., an uninvolved lymph gland immediately below the site of ligature).

TABLE I.—HIGH LIGATION OF MESENTERIC VESSELS IN 214 CASES OF CARCINOMA OF LEFT COLON AND RECTUM

Duke's classification		*Rectum and rectosigmoid*			
	Colon	*Combined excision*	*Anterior resections*	*Hartmann's excision*	*Total*
A	6	20	3		29
B	23	48	18		89
C_1	17	48	12	1	78
C_2	4	8	5	1	18
Totals	50	124	38	2	214

This may seem a poor return for the increased effort but it is pointed out that as the operation in the majority of C_2 cases was often palliative, because of distant metastases, high ligation was not performed. If it were not for this fact, the proportion of conversions following high ligation would undoubtedly have been higher.

Time only will tell the extent to which prognosis may be improved by this maneuver.

SUMMARY

Features in the surgical anatomy of the inferior mesenteric artery are re-emphasized, and their importance in the procedure of high ligation of the artery during operation for carcinoma of the rectum and colon is stressed. The technique for high ligation of the inferior mesenteric artery is outlined, and the results in 214 cases of carcinoma of the large intestine in which this procedure has been performed are discussed.

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ADRENALECTOMY IN ADVANCED MAMMARY CANCER

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CANCER OF THE BREAST accounts for approximately 25,000 deaths among women in the United States each year. The persistence of this high mortality rate and the relatively unchanging "cure" rates offered by the various methods of primary attack upon the tumor have led to increased emphasis on palliation and to research concerning methods of treatment of those lesions that cannot be considered curable. Indeed, the great numbers of patients dying from breast cancer each year has made effective palliative treatment a prime concern of cancer research.

Because the patient with a breast cancer is, in most cases, treated first by a surgeon, and the disease historically is considered in the realm of surgical discipline, it logically falls to the surgeon to care for and, if possible, palliate the disease in his patient with advanced mammary cancer. Superradical operations, local irradiation, chemotherapy, hormonal additive programs, and endocrine ablative procedures are all part of the present-day surgical armamentarium for treating a patient suffering with an extensive breast cancer. The various forms of treatment are often combined, so that the avenues of approach to the problem are legion, and it is difficult to evaluate the effectiveness of any single method. Nevertheless, of all the forms of palliative treatment for widespread breast cancer, endocrine ablative procedures have consistently given the highest percentage of success and the most profound remissions.

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Huggins (14) in 1951 demonstrated that gratifying remissions could be obtained by removal of the adrenal glands in patients suffering from advanced mammary cancer. His work was hailed as a valuable new clinical tool; in addition, the successful performance of adrenalectomy opened new avenues of investigation concerning the interrelationships of hormones and neoplasia.

Although the successes following adrenalectomy are most gratifying, the failures are doubly tragic. The physician is not only confronted by the bleak prospect of a patient terminally ill with cancer, but he has now produced Addison's disease in this patient. The seemingly inherent failures of palliation following adrenalectomy have led many surgeons to abandon the procedure and others to approach it with misgivings. However, the relatively constant remission rate of 40 per cent reported by most investigators has encouraged some surgeons to use the procedure empirically in the hope of benefiting the few and establishing criteria for the many. The original criteria of Huggins (16) having to do with cell type and other factors have been reviewed and followed by a great number of clinicians, but remission following adrenalectomy is still reported as occurring in less than one half of the cases.

We have attempted to study patients subjected to adrenalectomy in the hope of understanding the physiologic processes leading to remissions and, thereby, to establish criteria for the selection of patients to be treated by adrenalectomy. In this study, the patients were those whose ovarian function had been eliminated, so that only

the adrenal glands were removed. No other treatment was used so that adrenalectomy might be evaluated as an isolated procedure and an isolated physiologic event, in the hope of delineating its effects and indications. We have adopted the thesis that there must be some common denominator of success, so that this potent weapon can be reserved for those patients in whom there is a reasonable chance of success.

MATERIAL

All patients included in this study were inpatients at the University of Michigan Hospital. The University Hospital is a large general hospital whose patients are mainly referred from other facilities and come from the urban and rural centers throughout the State of Michigan. Therefore, most patients were seen by us only after the diagnosis of advanced mammary cancer had been made. The majority of the patients had received some prior treatment for the breast lesions. The patients were observed before and after treatment in a weekly clinic conducted by the authors at the Out-Patient Department of University Hospital.

Twenty-seven women suffering from advanced mammary cancer were subjected to simultaneous bilateral adrenalectomy. No other significant treatment had been given for the mammary cancer within 6 weeks before the adrenalectomy. In all patients who underwent adrenalectomy, the variable of ovarian function had been eliminated. Of the 27 patients included in this series, 18 had undergone previous bilateral oophorectomy, 7 had been subjected to x-ray castration by our standard "castration technique" (3) in which at least 625 roentgens are delivered to each ovary, and 2 of the patients were more than 18 years past the menopause. In this latter group, estrogen excretion studies indicated that what estrogen production remained was adrenal in origin and not ovarian. This aspect will be discussed in some detail later. By eliminating the variables of prior treatment and of ovarian function, we were then in a position to evaluate adrenalectomy as an isolated change in the endocrine environment of the host.

The presence of metastatic disease from breast cancer was established by routine clinical and laboratory procedures and confirmed by a tissue diagnosis whenever practicable.

METHODS

Preoperative evaluation. In all cases in this series, a tissue diagnosis of mammary cancer had been made from the original operative specimen or from biopsy material obtained in this hospital. These specimens were diagnosed and a description of the microscopic findings given by members of the Department of Pathology of the University of Michigan, but no single examiner reviewed all specimens. Records were made of the age of the patient, menstrual status, and the presence or history of hot flushes. Duration of disease was established as the time from the first sign or symptoms of the original tumor until the time of adrenalectomy. All patients had one feature in common—the carcinoma was far advanced, either locally or in a metastatic site, so that local irradiation or excisional therapy was not feasible.

In general, the criteria for selection of cases for adrenalectomy were: evidence of advancing disease and the lack of significant treatment for 6 weeks prior to adrenalectomy. Exceptions were made in certain cases in which local irradiation had been followed by the development of a more generalized disease. It was believed that these patients were candidates for the series in that the lesions that had not been treated could be used as indices of success or failure.

The response to previous treatment, whether additive or ablative hormonal therapy, was noted. The difficulties encountered in this phase of our preoperative evaluation will be discussed in detail later.

Stilbestrol stimulation tests and cortisone inhibition tests as described by Emerson and Jessiman were carried out in 6 of the 27 patients. Indices used were erythrocyte sedi-

mentation rate, C-reactive protein, the subjective response of the patient, and determinations of serum and urinary calcium after the patients were stabilized on a low calcium (120 mgm. per day) diet. Calcium determinations of the urine were done by the titration method of Clark and Collip and serum calcium determinations were done by the Beckman flame photometer using mixed standards containing sodium, potassium, and calcium.

Before the operation, serial determinations of 24 hour urinary estrogen excretions were made in all cases, 21 by both bioassay and chromatographic means, and 6 by bioassay only. By the bioassay methods, only total estrogen excretion is estimated, while in the chromatographic method, the fractions of estrone, estriol, and estradiol are determined and their sum is arbitrarily chosen as the "total estrogen excretion." The bioassay method was similar to that described by Smith and Smith, (26, 27) and chromatographic determinations were done by a modification of the methods of Zaffaroni and Bloch.

Preoperative preparation. Patients were prepared for operation in a routine fashion and the specific needs of the individual, such as transfusion and thoracentesis, were cared for. The patients received 50 milligrams of hydrocortisone every 6 hours on the day preceding operation, and, on the day of operation, 150 milligrams of hydrocortisone were given intramuscularly on call to the operating room. No hydrocortisone infusions were used before or during the operation.

Operation. In each case, both adrenal glands were removed in one operation. According to the surgeon's preference, the procedure was either carried out via the flank position (in which the patient had to be turned) or in the face down position advocated by Lapides. Recently, the preference in our hospital has been for the latter method since the patient need not be turned and two teams of surgeons can remove the adrenal glands simultaneously. Using this method, the procedure can be accomplished in slightly less than 1 hour.

Postoperative care. Following operation the patients are maintained on hydrocortisone, 50 milligrams intramuscularly every 4 hours for the first 24 hours. The dosage is then decreased in increments of 50 milligrams daily until the patient is on maintenance dosage. The maintenance dosage in most patients is 35 milligrams per day of hydrocortisone orally and 0.05 to 0.1 milligram of 9-alpha-fluro-hydrocortisone. Indices of proper maintenance are the absence of orthostatic hypotension, normal serum electrolytes, normal daily temperature, well-being of the patient, and stable weight and volume of urine. With experience, the adrenalectomized patient is readily managed by the physician familiar with the biologic properties of the corticosteroids.

Postoperative evaluation. Following operation, when the patient has been stabilized with maintenance doses of corticoids, estrogen excretions are again determined. Serum calcium, alkaline phosphatase, and blood counts are determined postoperatively if advisable. The operative specimens are examined by the pathologist to determine the presence or absence of metastatic tumor in the adrenal glands. The presence or absence of hot flushes is also noted.

So that our results would be comparable to others working in the field and that comparisons could be made on a concrete basis, only objective changes lasting for a period of more than 2 months were considered as remissions. These objective indices of remission were: measurable regression of all palpable or visible tumor masses; "bone healing" of the osteolytic lesions seen by x-ray examination; regression of pulmonary or pleural lesions by roentgenograms or the subsidence of chronic pleural effusion; and regression of retinal lesions seen through the ophthalmoscope. When there was no evidence of at least one of these objective improvements, the operation was considered a failure.

RESULTS AND DISCUSSION

Operative mortality and morbidity. Under the preoperative and postoperative program

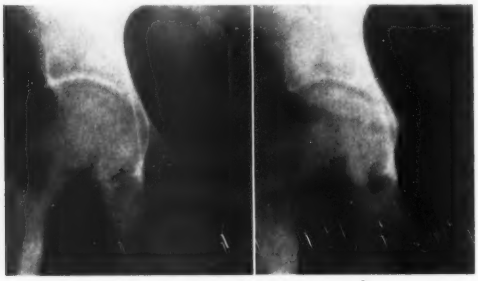

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FIG. 1. a, Preadrenalectomy and postadrenalectomy, b, roentgenograms of pelvis of a 58 year old negro female who experienced a profound subjective and objective remission for 12 months. Note sclerosis and new bone formation in the ischium following operation(b).

outlined, no operative deaths occurred in our series of 27 patients. That is, no deaths occurred within 30 days of the time of operation. This result compares favorably with a mortality rate of 13 per cent reported by Perlia and his co-workers, 5 per cent and 1.4 per cent as reported by Huggins (8, 16), and 5 per cent from the clinic of Sir Stanford Cade (5). There were 6 patients who had a significant postoperative complication. This gave a morbidity rate of 22 per cent. These complications included 2 wound infections (both of which were associated with operative or postoperative hemorrhage from the vena cava) and 4 episodes of postoperative adrenal insufficiency. Although 2 of the 4 episodes of insufficiency were severe, the patients responded well to large doses of hydrocortisone administered intravenously and intramuscularly.

Objective remission rate. The effect of adrenalectomy may be assessed by objective and subjective improvement or by the failure of the operation to benefit the patient. In patients who have a hormonally sensitive tumor, subjective relief is often immediate and profound. To the patient, the relief of pain or increased well-being is all important; obviously, subjective improvement is the important and deciding factor in the worth of the operation to the patient and her family. However, such subjective improvements cannot be measured, and an enthusiastic physician or a patient vainly trying to seek evidence of improvements will confuse the

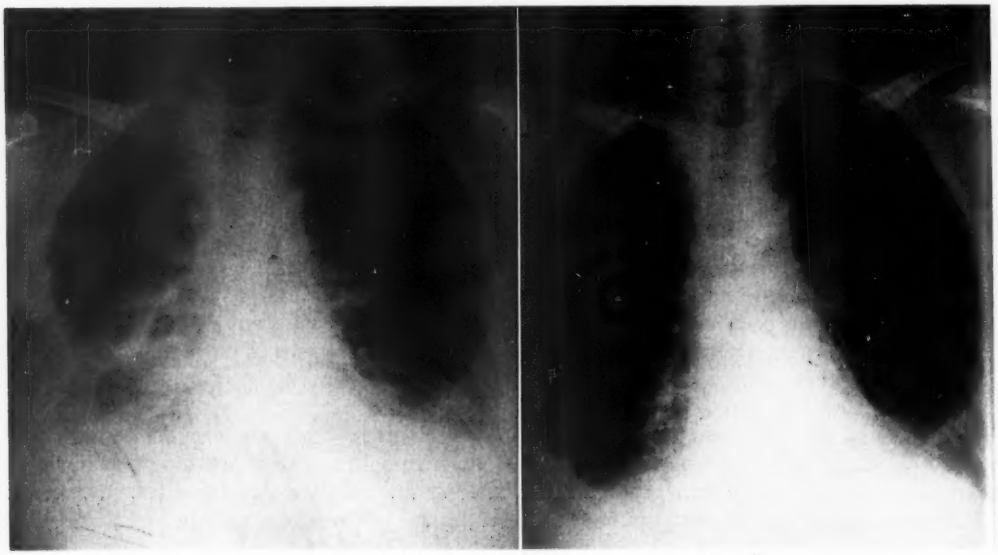

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FIG. 2. A 60 year old white female who has had clearing of bilateral pleural effusion and relief of dyspnea for 14 months following adrenalectomy. a, Preadrenalectomy and, b, postadrenalectomy films of chest.

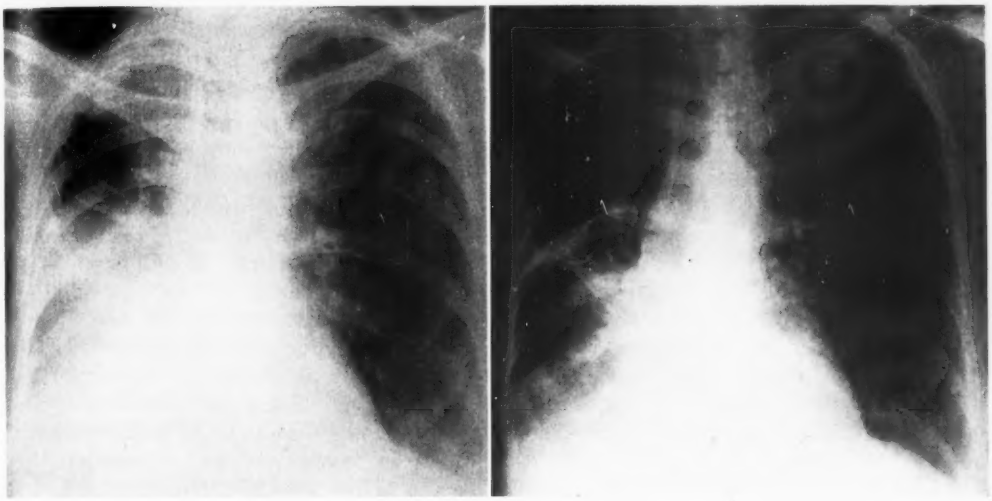

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FIG. 3. a, Preadrenalectomy and, b, postadrenalectomy films of chest of 47 year old white female who had objective remission for 9 months. Note clearing of right pleural effusion and the disappearance of 5 metastatic deposits from the lateral left lung field in the postoperative film.

issue so that we believe that subjective improvements must not be relied upon when assessing palliation in mammary cancer. We have, therefore, adopted objective indices as the only method whereby the benefit, if any, of adrenalectomy can be ascertained (Figs. 1, 2, and 3).

Of the entire group of 27 patients, 15 or 54.8 per cent received no benefit from adrenalectomy and were classified as failures. Twelve of the 27 patients experienced objective remissions (45.2 per cent). This corresponds well to the published figures of Cade (4, 6) who noted objective remissions in 39 per cent, Huggins (16), who observed remissions in 40 per cent, Delarue who reported "dramatic objective improvement" in 40.6 per cent, and Pearson (23) who achieved remissions in 45 per cent of the cases studied by the Memorial group. Perlia and Taylor reported that they observed "worthwhile palliation" in only 25 per cent of the cases studied. However, they did observe "objective regression of tumor" in 3 additional patients in the series of 50, but thought that the palliation achieved was not "worthwhile."

It is obvious, then, that in a random selection of postcastrational patients, adrenalectomy results in objective improvement in less than half of the patients treated. When subjective improvements are considered, the percentage rises greatly, but here the investigator is dealing with a factor that is not measurable and that varies from patient to patient and physician to physician.

Length of life and duration of remission. At the time of this writing, 8 of the 12 patients who experienced remissions are still living. One patient died of probable pulmonary embolus 2 months following operation and another patient died of adrenal insufficiency 2½ months after operation. In both of these patients, there were objective remissions prior to the time of death. Of the 15 patients who failed to be benefited by adrenalectomy, 12 have died. The average survival in this group was 4.2 months from the time of operation. The shortest survival period in this group was 2 months, the longest was 8 months. One patient is alive 6 months following a nonbeneficial adrenalectomy; this patient, however, underwent hypophysectomy subsequent to adrenalectomy and ap-

TABLE I.—AGE DISTRIBUTION

	Entire group	*Remissions*	*Failures*
No. of patients	27	12	15
Youngest, yrs. old	37	41	37
Oldest, yrs. old	61	61	58
Median age, yrs.	47	54	45
Average age, yrs.	48.5	53.5	44.7

pears to have benefited from the procedure. Two patients are alive, but in the terminal stage, 4 and 8 months after adrenalectomy.

Of the patients benefiting from adrenalectomy, 2 died of causes not directly related to the cancer, as mentioned before. The cause of death, however, was indirectly related to the operation, and these patients should be included in calculations of the life expectancy following adrenalectomy since future adrenalectomy patients will be subject to the same risks. The patients who benefited from adrenalectomy have had an average period of remission of at least 7 months. It should be noted, however, that exclusive of the 2 patients whose death was not due to cancer, the average remission was over 8 months. In addition, 7 of the 12 patients who underwent remissions are still in remission. Therefore, the absolute remission time cannot be accurately calculated at this time. One patient has gone 19 months in remission and 1 patient has gone 11 months. One patient was in remission for 12 months before succumbing rapidly to her disease. From these figures, it is judged that successful outcome of adrenalectomy does increase the life expectancy of these patients, since the remission time in such cases is twice the survival time for patients in whom adrenalectomy failed. This may, however, merely reflect the slower evolution of those tumors that are sensitive to estrogen withdrawal. However, these observations strongly suggest that successful adrenalectomy does increase life expectancy. Certainly it increases the period of clinical freedom from symptoms. Cade points out that the length of survival is not the only criterion for the value of adrenalectomy. The total period of survival can be subdivided into a phase of actual remission in the hormone sensitive tumors and a phase of further recrudescence of activity and decline. Huggins reported remissions ranging to 5 years, with an average of approximately 12 months, while Pearson has observed an average remission time of less than 7 months. Cade records data showing that most remissions are of less than 1 year's duration.

Correlation of age with remissions. In his original communication regarding adrenalectomy for breast cancer, Huggins (14, 16) pointed out that women in the menopausal years received, on the whole, benefit in a greater percentage of instances than did their younger or older counterparts. Cade (6), however, found no evidence of any difference between adrenalectomized women in the premenopausal and postmenopausal groups. However, both Huggins (15, 16) and Cade (5, 6) often combined oophorectomy with adrenalectomy, so that remissions could not properly be credited to one ablative procedure in preference to the other. Taylor and his group found that the best results could be expected in the 40 to 50 year age group. The combined results of Huggins (15, 16), Cade (4), Galante, Pearson (24), and Perlia indicate that women under 40 and women past 60 do less well following adrenalectomy than those women in the forties and fifties. Again, in these reports, oophorectomy was often combined with adrenalectomy so that absolute determination of the worth of adrenalectomy has only been suggested and not definitely established. In our series, the youngest patient was 37, and the oldest was 61. The youngest patient to benefit from the isolated procedure was 41 and the oldest 61. The average age for the series of patients was 48.5 years. The average age of those in the "successful group" was 53.5 years and the average age in the "failure group" was 44.7 years (Table I). It would seem, therefore, that while age is not an absolute criterion for adrenalectomy, the generalization can be made that younger patients as a group do not do as well following adrenalectomy as those patients in the 45 to 55 year bracket.

Duration of disease. It is assumed that the length of time a patient harbors a malignant disease is either an index of the malignancy of that particular tumor or a reflection of the host's resistance to the invader. In trying to establish criteria for adrenalectomy, both tumor malignancy and host resistance must be considered. Therefore, some estimation of the duration of the disease process is essential. We believed that in our study it was impossible to define in a single patient at a given moment the phase of the disease that had been reached. Therefore, we arbitrarily chose as a measurement of the duration of disease the time from the first sign or symptom of the tumor to the time of adrenalectomy. Granted, some patients may undergo adrenalectomy far earlier in their history than others. However, by applying this measurement to all patients, some degree of uniformity can be achieved. Pearson (20) and his co-workers have adopted the same plan of estimation of duration of the disease. Huggins (16) has shown that better results can be expected in those patients who had a prolonged interval between mastectomy and onset of clinically demonstrable recurrent or metastatic disease. In a comparison of the data of Huggins and Taylor, Taylor (25) showed only a 12 per cent remission rate in those who had had disease of less than a year's duration, while 54 per cent of those individuals who had the disease for over 5 years experienced remissions.

In our series, with duration of disease defined as the period from the time of onset until the time of adrenalectomy, the average duration of disease was slightly over 41 months. In those patients who benefited from adrenalectomy the average duration was 63.3 months, a range of from 4 to 204 months. In those who were not benefited, the shortest duration was 12 months and the longest 72 months; average duration was 31.2 months. The average figures of 31 months for "failures" and 63 months for "successes" corresponds remarkably to that of Pearson (20) who reported average figures of 33 and 63 months respectively (Table II). It can be seen from these figures that duration of the disease as an indication of either the malignancy of the tumor or the defense of the host has in general a direct relationship to the success of palliation following adrenalectomy. Unfortunately for those seeking absolute criteria, duration of disease does not appear to be a specific index since there is considerable overlapping in our series and in those reported by others. In our series, both the shortest and longest histories were associated with successful palliation following adrenalectomy. It is of interest to note that the patient with the shortest history had an inflammatory carcinoma of only 4 months' duration and achieved remarkable palliation from adrenalectomy. One can postulate that when dealing with an inflammatory carcinoma we are perhaps not dealing with an inherently vigorous neoplasm, but a neoplasm that is caused to flourish by the high estrogen level of the host.

TABLE II.—DURATION OF DISEASE

	Entire group	*Remissions*	*Failures*
No. of patients.....	27	12	15
Shortest period, mos.....	4	4	12
Longest period, mos.....	204	204	72
Median period, mos.....	36	20	18
Average period, mos.....	41.03	63.3	31.2

Response to previous therapy. Conflicting experiences pervade the literature as to the reliability of selecting candidates for adrenalectomy on the basis of their response to previous therapy. Pearson (22, 23) and associates suggest that those patients who fail to respond to oophorectomy will also fail to achieve palliation by adrenalectomy. Perlia and Taylor were unable to correlate the response to previous therapy—either ablative or additive—with the response to adrenalectomy. Cade (6) found a good correlation between prior additive therapy (androgens or corticoids in this case) and subsequent remissions after combined oophorectomy and adrenalectomy. However, here we are again faced with the insoluble problem of isolating the effect of one procedure when two glandular ablations have

been combined. MacDonald correlates success after adrenalectomy with response to previous castration in the premenopausal group and remissions with additive therapy (estrogens) in the postmenopausal patients. He bases his selection of hormone sensitive tumors on the premise that specific addition or withdrawal is not the prime factor in palliation, but that a mere change in the hormonal environment is sufficient to effect remissions in the proper tumor.

In attempting to evaluate responses to previous therapy, we were confronted with a threefold problem: (1) patients often had additive regimens of more than one hormonal or chemotherapeutic agent; (2) the attempts at previous palliation were often made via homeopathic amounts of steroids that we did not consider to be significant; and (3) in most cases, objective evidence was not obtainable either prior to or following the additive measures applied to our patients. Moreover, all but 1 of our patients had received the additive treatment elsewhere. It was impossible, in the face of these obstacles, to make an accurate evaluation of the role of additive therapy in our patients. It is of interest to note that we encountered several patients who gave a history of a significant increase in symptoms following the administration of 1 or 2 "shots" of an androgen. We have been impressed by the uniformity of this finding and interpret this to represent the conversion of androgens to estrogens as described by Dorfman (1).

Of the group of 27 patients, 18 had undergone therapeutic castration. The remainder of the group were either 18 years or more past the menopause or had undergone castration as a prophylactic measure or for gynecologic diseases. Of the 18 patients who had been therapeutically castrated, 7 had undergone x-ray castration by our standard "castration technique." Eleven had been treated by bilateral oophorectomy. Among the 18 patients, 5, or 27.7 per cent, had experienced objective remissions following castration. Of those patients who subsequently benefited from adrenalectomy, 7 had undergone therapeutic castration. Four of this latter group (57.1 per cent) were benefited by castration. In the remaining 3 patients who received no benefit from castration but who later received remissions with adrenalectomy, it was found that their estrogen excretion did not decrease after castration. We interpreted this to mean that we had not eliminated the source of estrogens by castration and that the adrenals were the source of estrogen. All of these 3 patients showed a decrease in estrogen excretion when they finally underwent adrenalectomy.

In considering the 11 patients who subsequently failed to have a remission following adrenalectomy, only 1 had received benefit from therapeutic castration. This 1 patient who was benefited by castration did not have significant estrogen excretion at the time of the fruitless adrenalectomy.

From these observations, we conclude that if castration is of benefit to the patient, in the majority of cases she will be benefited by subsequent adrenalectomy. Conversely, if castration resulted in a fall in the estrogen excretion without benefit to the patient, then the patient will not receive benefit from adrenalectomy and should not be considered as a candidate for the operation. It is important to note that we believe that estrogen excretions remaining high after castration makes an evaluation of the hormonal sensitivity of the tumor an impossibility. In that case, all that we can conclude is that the ovaries were not the site of estrogen production to a significant degree and that castration did not alter the environment of the host. In these cases, no results could be expected from castration.

Stimulation tests as a prognostic method. Pearson (22), Laszlo, and Emerson advocate the use of stilbestrol stimulation tests in those individuals who are to be considered for adrenalectomy. The basis of this test was the observation by Sir Astley Cooper in 1836 and again by Pearson (22) in 1953 that there seems to be increased metabolic activity of mammary tumors during the

menstrual period. Attempting to quantitate this response to changes in the estrogen environment, Pearson and Emerson determine certain measurable metabolic phenomena such as the blood levels and the urinary excretion of calcium. After a baseline determination of this is done, stilbestrol is given and changes in the blood and urinary calcium are observed. This test has been further amplified to include sedimentation rate, increased pain, and clinical well-being of the patient as an index of stimulation of the tumor by the added synthetic estrogen. Both Pearson and Emerson have been impressed by the use of this test as a means of predicting the effectiveness of adrenalectomy. In addition, the reverse of this test (using cortisone to inhibit the adrenal production of estrogens) is advocated in castrate females to determine the advisability of proceeding with adrenalectomy.

It is well known that from 50 to 75 per cent of women with metastatic mammary cancer have osseous metastases. However, hypercalcemia is found only in from 9 to 18 per cent of the patients. The response to the metastatic bone deposit varies from one patient to another in that the reparative process, bone destruction, and changes in alkaline phosphatase levels vary greatly from patient to patient and in given individuals from time to time. In our series, 12 (or 45 per cent) of the patients had known osseous metastases. Of these patients, only 4 (or 14.8 per cent) had demonstrable hypercalcemia when first seen by us or when first considered for adrenalectomy.

In 6 of the 27 patients stilbestrol stimulation tests were carried out, and in 2 patients cortisone inhibition tests were conducted. In these tests baseline C-reactive proteins, erythrocyte sedimentation rates, and serum and urinary calcium levels were determined after the patient had been on a diet restricted to 120 milligrams of calcium per day for at least 3 days. In the stilbestrol stimulation tests, 15 milligrams of stilbestrol were given daily for a period of from 3 to 5 days. Observations were made of the values mentioned for at least 5 days following the administration of stilbestrol. In only 1 case was there suggestive evidence that the tumor was sensitive to the administration of stilbestrol. This patient subsequently experienced remission following adrenalectomy. In the other 5 cases, no interpretation of the test was possible. In addition to the 6 tests reported here, we have run stilbestrol stimulation tests on 25 other patients. In these individuals we were impressed by the lack of uniformity of results, with changing calcium excretion from day to day and apparent lack of correlation with the administration of stilbestrol. The C-reactive protein and erythrocyte sedimentation determinations did not show any changes with stilbestrol administration. The subjective condition of the patients varied greatly with the administration of stilbestrol so that they were impossible to interpret. There was, however, a high incidence of nausea associated with the ingestion of oral stilbestrol.

The cortisone inhibition test was more rewarding in the 2 patients in whom it was tried. The test is similar to the stilbestrol stimulation test except that cortisone is administered in the amounts of 100 to 150 milligrams per day. The observations recorded are similar to the stilbestrol stimulation test. With this test we had 1 positive and 1 negative reaction. That is, 1 patient showed a decrease in the urinary calcium that we thought significant and the other patient showed no change. The patient who had no change did not receive benefit from adrenalectomy while the patient who had a positive test achieved a dramatic remission for 12 months.

In general, we believe that the stilbestrol stimulation test, although occasionally giving interesting correlation with the final outcome, is of no value as a routine clinical procedure to select patients for adrenalectomy. In addition, the number of patients suffering from actual hypercalcemia and calcinuria reduce the applicability of the test. The cortisone inhibition test will be

TABLE III.—RELATIONSHIP OF RESPONSE TO MORPHOLOGY OF TUMOR AND CLINICAL SITE OF METASTASES

		Metastatic site					
	Tumor type	*Pleura, lung*	*Liver*	*Brain*	*Skeleton*	*Eye*	*Local soft tissue*
Remissions							
1	S-A	x					
2	S-A	x			x		
3	S-A	x					x
4	M-S-A				x		x
5	A-Gr3		x		x		
6	A-Gr3-I	x					x
7	S-A Gr4						x
8	S-M				x		
9	S						x
10	S-A				x		
11	A				x		
12	A	x					x
Failures							
1	A-Gr4	x	x				x
2	A						x
3	A	x	x				
4	S-A	x			x		
5	A	x	x				
6	A	x	x	x			x
7	A-Gr4	x					x
8	A-Gr4						x
9	M-S				x		
10	S-A	x			x	x	
11	S-A	x	x		x		
12	S-A	x			x		
13	S-A	x		x	x		x
14	A						x
15	A	x					x

A—adeno
S—scirrhous
M—medullary
Gr—grade
I—inflammatory

evaluated further before definite conclusions are drawn. However, the lack of correlation in the percentage of remissions between the so-called "medical adrenalectomy" and operative removal of the adrenal glands would make one believe that this test also will be discarded as a routine method of selecting patients for adrenalectomy.

We have not found the C-reactive protein or erythrocyte sedimentation rate to be of value in following either the regression or progression of the disease following adrenalectomy.

Histologic characteristics of the tumor and location of metastases. In the majority of reports, the original criteria of Huggins (16) have stood the test of time with the exception of the correlation of response to adrenalectomy with the histologic characteristics of the tumor. Huggins' original observation that those tumors composed of "spheroidal cells with acini having lumina whose lining is one cell thick" were responsive to hormonal changes have been challenged by several authors. Cade (6), Taylor (25), Pearson (22), and Kennedy all believe that histologic grading is not a reliable means of predicting tumor characteristics. Mammary tumors are notoriously multimorphous, and classification of these tumors is difficult and varies from one pathologist to another. As seen in Table III, there was a wide range of morphologic diagnoses associated with both the remission and failure groups in our study.

Cade (6) has found both hormone dependence and independence for skeletal, visceral, cutaneous, and primary tumor deposits. He has achieved striking regressions of tumor in skeleton, liver, lungs, pleura, skin, and in the eye. Pearson (22), on the other hand, has not been impressed with the success of adrenalectomy following the demonstration of hepatic metastases. Table III shows the occurrence of metastases in the success and failure groups according to the area of clinically determined metastases. Metastatic deposits were grouped as

TABLE IV.—PREOPERATIVE AND POSTOPERATIVE ESTROGEN EXCRETIONS IN PATIENTS SUBJECTED TO BILATERAL ADRENALECTOMY

	Estrogen excretion							
	Preoperative				*Postoperative*			
Patient	*Total*	*E1*	*E2*	*E3*	*Total*	*E1*	*E2*	*E3*	*Remission*
G. B.	3.2	2.0	0.8	0.4	0.47	0.3			Yes
M. D	5.5	1.9	0.8	2.8	0.91	0.24	0.4	0.27	No
A. E.	4.25	3.2	0.32	0.73	0.58	0.3	0.28	....	Yes
L. F.	1.9	1.6	0.3	....	0.26	0.26	....	....	Yes
B. F.	0.78	0.56	....	0.22	0.77	....	0.51	0.26	No
A. G.	3.8	2.8	0.7	0.3	1.0	1.0	....	....	Yes
S. J.	1.6	1.6	....	....	0.5	....	0.5	....	Yes
R. L.	1.8	1.8	....	....	0.48	....	....	0.48	Yes
V. L.	1.6	0.67	0.65	0.28	0.22	0.17	0.05	....	Yes
A. P.	6.0				<2	0.11			Yes
J. R.	1.87	1.5	....	0.37	1.17	....	....	1.17	No
E. S.	0.90	0.62	0.24	0.04	0.13	0.13	....	....	No
A. S.	5.0	5.0	....	....					Yes
S. W.	1–1.5				none detectable				No
V. C.	1.7	1.4	....	0.3	<2 no trace				No
R. D.	<2				<2				No
C. D.	5.0				<2				Yes
M. G.	1–2				<1				No
V. G.	0.8	0.2	0.3	0.3	0				No
L. H.	6.6	2.2	1.4	3.0	0.44	0.26	0.18	....	Yes
S. M.	4.13	1.2	2.9	0.2	0.3	0.3	....	....	No
I. R.	<2				<2				No
V. S.	4.0	2.6	....	.?..	<2				No
M. S.	<2				expired				No
A. S.	10.7	4.1	4.1	2.5	<2				Yes
C. S.	<2	0.8			<2				No
D. Y.	5.0	2.6	....	....	1.9	1.2	0.64	0.04	No

E1—Estrone, E2—Estradiol, E3—Estriol.
< less than 2 micrograms or "rat units."

pleura and lung, liver, brain, skeleton, eye, and local soft tissue. Pleural and pulmonary deposits, skeletal involvement, and occurrence of large thoracic wall and axillary soft tissue deposits appeared to have equal distribution among the successful and unsuccessful cases. In the 2 cases with obvious cerebral involvement, there was no remission following adrenalectomy. In the 6 cases with clinically demonstrable hepatic involvement, there was only 1 patient who benefited from adrenalectomy. We believe from this observation that massive hepatic or cerebral metastases are contraindications to the operation. We admit that it is possible for remissions to occur with metastatic involvement in these areas but the odds are slight and do not warrant the gamble in most patients!

Preoperative and postoperative estrogen excretion. Of the 27 patients in this series, all but 2 had been castrated either by irradiation or by operation prior to adrenalectomy. The other 2 patients were more than 18 years past the menopause and estrogen excretions indicated that what estrogen production remained was not ovarian in origin and was, perhaps, solely from the adrenal glands. In these 2 patients, estradiol was present in only minute amounts in the serial urine specimens and estrone and estriol (considered to be primarily adrenal in origin) were the only detectable estrogens. It seemed apparent that in these 2 patients the adrenals were the course of the urinary estrogens and that subjecting these patients to castration would only be meddlesome intervention for the sake of a complete series (Table IV).

In the early portions of this study, estrogen excretion was measured by a method of bioassay according to Smith and Smith (26, 27). The minimal positive response is "less than 2 rat units—trace." We have found that a completely negative response in bioassay determinations corresponds to 1 microgram of total estrogen as determined by chromatography. Recently, we have

TABLE V.—RELATIONSHIP OF RESPONSE TO DECREASING AMOUNTS OF ESTROGEN EXCRETION

Total estrogens micrograms	*Response*	*Estrone micrograms*	*Response*	*Estradiol, micrograms*	*Response*	*Estriol, micrograms*	*Response*
10.7	Success	5.0	Success	4.1	Success	3.0	Success
6.6	Success	4.1	Success	1.4	Success	2.5	Success
6.0	Success	3.2	Success	0.8	Success	2.8	Failure
5.5	Failure	2.8	Success	0.8	Failure	0.73	Failure
5.0	Success	2.6	Failure	0.7	Success	0.4	Success
5.0	Failure	2.6	Failure	0.65	Success	0.37	Failure
5.0	Success	2.2	Success	0.32	Success	0.3	Success
4.25	Success	2.0	Success	0.30	Success	0.3	Failure
4.0	Failure	1.9	Failure	0.30	Failure	0.3	Failure
3.8	Success	1.8	Success	0.24	Failure	0.28	Success
3.2	Success	1.6	Success			0.22	Failure
1.9	Success	1.6	Success			0.04	Failure
1.87	Failure	1.5	Failure				
1.8	Success	1.4	Failure				
1.6	Success	0.8	Failure				
1.6	Success	0.67	Success				
1.5	Failure	0.62	Failure				
1.0	Failure	0.56	Failure				
0.9	Failure	0.2	Failure				
0.8	Failure						
0.78	Failure						
<2 no trace	Failure						
<2 no trace	Failure						
<2 no trace	Failure						
<2 no trace	Failure						
<2 no trace	Failure						
<2 no trace	Failure						

relied on paper chromatography to determine total estrogens composed of the fractions of estrone, estriol, and estradiol.

Preoperative total estrogen excretion. A fall in the total estrogen excretion was noted between preoperative and postoperative determinations in all but 3 of the patients in our series (Table IV). In these 3 patients, preoperative determinations by the bioassay method were below the level of sensitivity and, therefore, no fall could be demonstrated.

An analysis of the preoperative total estrogen excretion shows that of the 11 patients in whom the preoperative total estrogen excretion was below a total of 1.5 micrograms per day (or no trace on bioassay) there was no instance of remission following adrenalectomy (Fig. 4). Among the group in whom preoperative estrogen excretion was above 1.5 micrograms per day, remissions were noted as follows: 1.5 to 2.0 micrograms, 4 of 5 patients; 2.0 to 5.0 micrograms, 3 of 4 patients; and in those patients whose total excretion was in excess of 5.0 micrograms per day, 3 of 4 patients experienced remissions. After the seemingly critical plateau of 1.5 micrograms of total estrogen excretion was reached, the remission rate in all groups was between 70 to 75 per cent (Tables V and VI).

Preoperative estrone excretion. Chromatographic determinations of estrone excretion were carried out in 19 patients prior to operation (Table IV). The lowest estrone excretion associated with postoperative remission was 0.67 microgram per day. One of the 5 patients whose estrone excretion was between 0 and 1 microgram per day underwent a postoperative remission (20 per cent). Between 1.0 and 2.0 micrograms of estrone excretion, 4 of 7 patients experienced remissions (57.1 per cent). Five of the 7 patients whose estrone excretion was in excess of 2.0 micrograms per day experienced remission (71.4 per cent) (Fig. 5).

Preoperative estriol excretion. Both success and failure were encountered at relatively low levels of estriol excretion (Tables IV and V, Fig. 6). In all, the preoperative estriol excretions were determined in 12 patients. Among the group in whom preoperative estriol excretion was between zero and 1.0 microgram, remissions were

noted in 3 of the 9 patients (33 per cent). Of the 3 patients whose estriol excretion was between 1.0 and 3.0 micrograms, 2 underwent postoperative remissions. Considering the excretions according to frequency groups, we note that there was a 33 per cent remission rate between zero and 0.3 microgram, 50 per cent between 0.5 and 3.0 micrograms, and 66 per cent between 1.0 and 3.0 micrograms.

Preoperative estradiol excretion. Preoperative estradiol excretions were measured in 10 patients (Table V). Again, success and failure were encountered at relatively low levels of estradiol excretion. Between zero and 0.5 microgram of estradiol excretion was associated with remissions in 2 of the 4 patients (50 per cent). Three of the 4 patients whose excretion was between 0.5 and 1.0 microgram experienced remissions after operation (75 per cent). The 2 patients who excreted more than 1.0 microgram of estradiol in 24 hours both experienced postoperative remissions (Fig. 7).

We are considering a problem in which minute amounts of estrogen are measured. The possibility of error therefore is great. For this reason and because of the very nature of the disease in question, a much larger series than we have presented must be collected if valid conclusions are to be made.

Since we have altered only the endocrine environment of the host by removing the adrenals, after eliminating the possibility of ovarian function, we have assumed that any difference in preoperative and postoperative determinations of estrogen excretion reflected a decrease in adrenal estrogens. Engel has stated that estradiol is primarily a gonadal estrogen, although small amounts of this most active steroid are manufactured in the adrenals. Estrone and estriol, on the other hand, are primarily adrenal in origin. Therefore, in considering patients more than 18 years past the menopause who have low estradiol excretions and significant excretions of estrone or estriol, we can reasonably assume that estrogen production is taking place in the adrenal glands and not in the gonads. In other work, we (3) have demonstrated as have others that the possibility of postmenopausal ovarian production of estrogens is real and great, and, therefore, larger amounts of estradiol excretion alert us to the possibility of functioning ovaries in this senile group.

There appears to be a critical level of between 1.5 and 2.0 micrograms of total estrogen excretion which must be present in order for adrenalectomy to benefit the patient. Below this level, no patient in our series received any benefit from the procedure. Above this level, regardless of the magnitude of the excretions, about two-thirds to three-quarters of the patients received remissions. This observation would indicate that minute amounts of total estrogens, as reflected by the urinary excretion, are not sufficient to maintain an endocrine-sensitive tumor, and that attempts at palliation by ablative therapy in this group are probably hopeless.

TABLE VI.—PREOPERATIVE ESTROGEN EXCRETIONS

	Total estrogen micrograms/24	*Estrone micrograms/24*	*Estridiol micrograms/24*	*Estriol micrograms/24*
Remissions				
1	3.2	2	0.8	0.4
2	4.25	3.2	0.32	0.73
3	1.9	1.6	0.32	....
4	3.8	2.8	0.7	0.3
5	1.6	1.6	....	....
6	1.8	1.8	....	....
7	1.6	0.67	0.65	0.28
8	6.0			
9	5.0	5.0		
10	5.0			
11	6.6	2.2	1.4	3.0
12	10.7	4.1	4.1	2.5
Failures				
1	5.5	1.9	0.8	2.8
2	0.78	0.56	...	0.22
3	1.87	1.50	...	0.37
4	0.90	0.62	0.24	0.04
5	<2			
6	1.5	1.4		0.3
7	<2			
8	1.0			
9	0.8	0.2	0.3	0.3
10	<2			
11	<2			
12	4.0	2.6		
13	<2			
14	<2	0.8		
15	5.0	2.6		

Blanks indicate no determination.
... indicates no estrogen fraction separated.

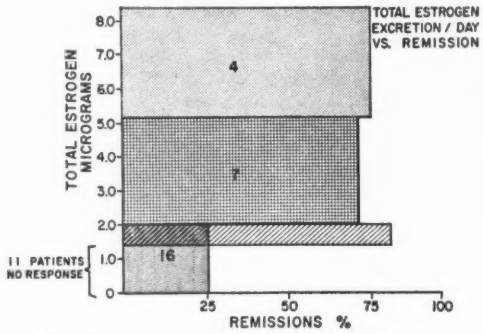

FIG. 4. Remission rate versus preoperative total estrogen excretion per day.

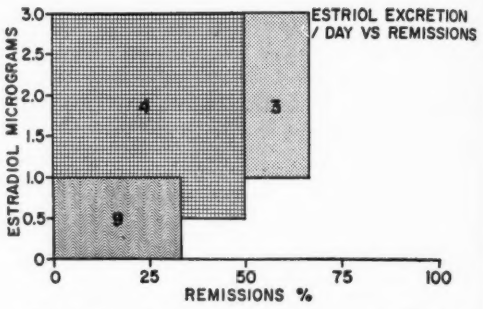

FIG. 6. Remission rate versus preoperative estriol excretion per day.

Estrone and estriol excretions appear to represent the magnitude of adrenal activity. The magnitude of their excretion bears almost a linear relationship to the success of adrenal ablation. Although only very small amounts of each were present in some of the successful cases, there is an indication that the two measured fractions taken together combine to effect a favorable tumor environment. Increasing amounts of estrone or estriol excretion presaged a successful outcome for palliation by adrenalectomy in the majority of the patients followed up after castration.

Estradiol determinations also had a linear relationship to the success of adrenalectomy. Perhaps this again signifies the amount of estrogen production of the adrenal glands. It is reasonable to assume that increasing amounts of estradiol in a castrate female would indicate adrenal activity and, therefore, a greater probability of remission with adrenal ablation. Our estradiol determinations do not correlate well with estrone or estriol excretions and do not permit conclusions based upon their measurement.

From our data, we were unable to recognize evidence suggesting suppression of human breast tumor growth by the presence of higher levels of estriol. The demonstration of interference with estrone-stimulated uterine growth by high doses of estriol and other members of the estrane series with oxygenated functions at sites 6 or 16 may indicate

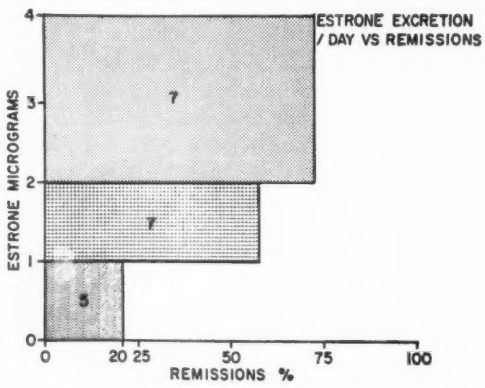

FIG. 5. Remission rate versus preoperative estrone excretion per day.

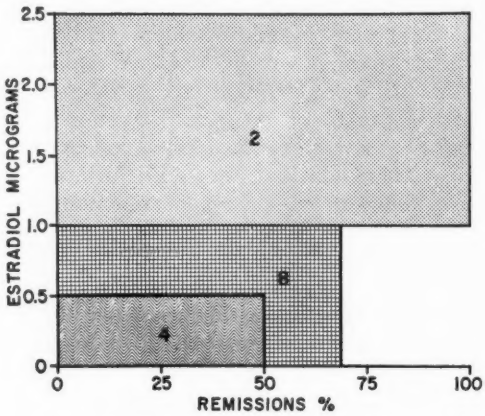

FIG. 7. Remission rate versus preoperative estradiol excretion per day.

that such a situation may be true of human breast carcinoma.

Adrenal metastases and postoperative "hot flushes." The surgeon who routinely practices ablative treatment for mammary carcinoma is soon made aware of the tendency for mammary tumors to metastasize to the ovaries or the adrenal glands. Huggins (16) reports that one-third of his patients had demonstrable metastases to the adrenal glands at the time of adrenalectomy. Huggins and Dao (16) demonstrated that 5 of 24 patients undergoing oophorectomy for palliation had microscopic foci of metastatic disease in the ovaries. It is intriguing to speculate as to the cause of this seemingly selective phenomenon of ovarian and adrenal metastases in far-advanced mammary cancer. One can assume that the patient who suffers from widespread disease has had at one time a shower of malignant emboli in the lymph and blood streams. Why then is there selective growth in the glandular structures that produce steroids? A tempting explanation is that the mammary tumor emboli are able to grow and multiply in these glandular structures because here is a medium high in steroids. We, therefore, investigated the advisability of prognostication on the basis of the presence or absence of adrenal metastases.

Random sections of the adrenal glands demonstrated metastatic disease in 12 of the 27 patients subjected to adrenalectomy (44.4 per cent). Among those patients who eventually achieved remissions from the disease, metastases had occurred in one-half of the cases (6 of 12); however, 6 of the 15 patients who eventually were classified as adrenalectomy failures had adrenal metastases (40 per cent). Therefore, on the basis of this random selection in a relatively small series, we are not able to correlate adrenal metastases to subsequent success or failure of adrenalectomy.

Huggins (16) also believed that post-adrenalectomy "hot flushes" similar to those of the menopausal syndrome were good prognostic signs. Eleven of our 27 patients experienced typical "hot flushes" usually in the upper portion of the body following adrenalectomy. Of these patients, 8 experienced remissions and 3 were classified as failures. There was no correlation between success or failure and the degree of decline in estrogen excretion following adrenalectomy. Serotonin degradation products were not measured in these patients either before or after operation. Hot flushes developing after adrenalectomy appear to constitute a rather favorable prognostic sign. No attempt is made to explain the mechanism of their occurrence other than the well-known association with decreasing circulating estrogens.

SUMMARY AND CONCLUSIONS

Huggins (13) has stated: ". . . it is safe to say that when a satisfactory elucidation of cancer has been made, the hormones will be found to occupy a position near the center of the problem. Hormones are significant factors in the etiology of cancer, its prevention and its treatment." The endocrine treatment of mammary cancer rests upon the concept of hormonal dependence and the withdrawal of hormonal substances thus altering the internal endocrine environment of the host. Probably nothing is accomplished by adrenalectomy that will alter in any way the inherent biologic properties of the tumor itself. The tumor-host relationship is altered and this at times effects control of the neoplastic disease by physiologic means. However, as Huggins states, the end result is merely control and has never been shown to be a cure. The tumors at best undergo remission followed inevitably by reactivation and death. Nevertheless, many of the remissions are dramatic and profound and persist for months or years.

With the idea firmly in mind that the therapy we offer the patients will not alter the eventual outcome and only at best offer palliation, we have sought to establish firm criteria for the selection of candidates. First, we have adopted most vigorous

standards for determining the occurrence of remissions. We have sought to isolate the physiologic and therapeutic effects of adrenalectomy by considering only those patients whose ovarian function has been ablated so that a second variable—that of ovarian function—will not be introduced into the biologic system under investigation.

We have found that the preparation of the patient for adrenalectomy, the performance of bilateral adrenalectomy in the severely ill patient, and the maintenance of the patient postoperatively are readily achieved by the surgeon willing to study the physiologic and biochemical alterations that he has engendered. The operative mortality is nil, and the postoperative complications, although present, are readily treated and of no lasting import.

In general, the patients who receive benefit are usually in their fifties. The majority of the younger patients do not have remissions following adrenalectomy. However, there is great overlap in the age groups, so that age by itself is not a determining factor. It should be considered, however, in the light of other findings.

The activity of the tumor and the resistance of the host is reflected in the duration of the disease up to the time of adrenalectomy. In common with other reports, the successful outcome of adrenalectomy frequently followed a prolonged duration of disease. This again is not determinate and must be considered as only part of the total clinical evaluation of the patient.

The stilbestrol stimulation test has not proved to be of value in our hands for the routine clinical screening of patients. The cortisone inhibition tests must be evaluated further. We have been unable to make any correlation between success or failure of adrenalectomy and the response to the administration of androgenic or estrogenic substances. However, response to previous therapeutic castration seems to be an excellent guide in the choice of the patient for adrenalectomy. Those patients who have been therapeutically castrated and who exhibit objective regression of the disease have already demonstrated the hormone-sensitive nature of the tumor. If, however, these patients fail to respond to oophorectomy, one must look further to see if the estrogen excretion fell after ablation of the ovaries. If this did not occur, castration did little to alter the host's environment and the response to castration cannot be considered as an index of the estrogen dependency of the tumor.

The morphology of the tumor or the location of the metastatic deposits bore little relation to the outcome of the operation, with the sole exception of hepatic involvement. Should the liver be obviously involved, by clinical evaluation, the operation is doomed to failure in a high percentage of the patients considered. This fact apparently reflects either profound damage to the liver that is incompatible with life or some change in the metabolism of estrogens brought about by destruction of liver tissue.

The determination of the preoperative estrogen excretion—both total estrogen and its fractions—appears to be the second solid basis on which to predict the success or failure of the operation. The lack of response in those individuals with low preoperative estrogen excretions and the increasing percentage of success in patients with a high preoperative excretion have caused us to recommend the operation only in those individuals with a significant estrogen excretion on several determinations prior to operation. Indeed, from the small series presented here, it is reasonable to assume that success can be achieved in roughly two-thirds to three-quarters of the patients if the operation is restricted to those who excrete relatively large amounts of urinary estrogen. We believe that our over-all remission rate being higher than that usually reported is a reflection of our selection of "high estrogen" patients toward the end of the series. It is reasonable to assume that tumors flourishing in a climate of high estrogen concentration may likely suffer from a reduction of this concentration, and that

tumors thriving in a medium almost devoid of estrogen will not be greatly affected by further decreasing the hormone. These data, however, need amplification before a definite rule of selection may be made.

We have shown that a rather random selection of patients for adrenalectomy will produce remissions in over 40 per cent of the patients. This is a reflection of the chance association of patients who have hormonally sensitive tumors and whose internal endocrine environment is conducive to the sustenance of these sensitive tumors. By careful selection of the patients on the aforementioned bases, a remission rate almost double that of the random selection can be achieved. That this remission rate is real and worthwhile is demonstrated by the fact that many remissions were months and years in duration. This is further attested to by the fact that the remission time alone in our series (including patients who have not yet run the full course of their remission) was twice that of the total life expectancy of the group in which remissions were not achieved.

We are dealing with an eventually fatal disease. Our treatment is one of palliation and not of cure. The nature of adrenalectomy is such that when success is not achieved, the surgeon and the patient are not left with a situation that remains in *status quo*. Instead, they are confronted with induced Addison's disease in the face of an advancing lethal neoplasm. In addition, they have invested time, effort, money, and pain in a fruitless effort. Therefore, on the basis of the findings presented we can recommend adrenalectomy only for those patients who fulfill most of the following criteria: (1) tumor not involving the liver; (2) previous remission from oophorectomy; (3) high estrogen excretion; (4) "middle age" (preferably 50's); (5) prolonged duration of disease (over 3 years).

As in any other set of clinical rules, individualizations must be made. However, when considering the patient for adrenalectomy, all of these facts must be considered individually and in light of each other. After 7 years, great trial and many investigations, the reader is impressed with the validity of the original observations made by Dr. Huggins.

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THE EFFECT OF ARTERIAL, VENOUS, AND ARTERIOVENOUS OCCLUSION ON RENAL BLOOD FLOW

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THE EFFECTS of temporary arterial and venous occlusion in certain areas of the body have become a problem of great importance. The various parameters involved must be evaluated because of the extensive surgical procedures requiring temporary circulatory stasis to portions of the body. The reactions of organs and organ systems to prolonged circulatory arrest may reveal some of the factors involved in the development of irreversible oligemic shock. Morris and his associates have studied this problem in animals using classical methods of measuring renal blood flow that depend upon renal function. We have been particularly interested in methods that do not depend upon renal function with the attendant inaccuracies that may be associated with any blood flow measurement that requires a normally functioning organ. We have also been interested in methods that do not require use of heparin, as it has been shown to alter the vascular reactivity of organs.

PURPOSE OF STUDY

The present study deals primarily with the effect of temporary circulatory stasis on blood flow in the kidney of the dog. This organ was selected in view of the fact that many surgical procedures upon the aorta result in the temporary interruption of renal blood flow.

METHODS

Adult mongrel dogs were anesthetized with pentobarbital, and midline laparotomy incisions were made.

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The left kidney was selected for study because of the length of its pedicle and because the liver does not interfere with the dissection and suspension of that kidney. The kidney was dissected free from its peritoneal attachments and was denervated as far as was surgically feasible. The renal artery and vein were dissected free from all tissues throughout their entire length. The ureter was isolated in a similar manner or cut. After the intestine had been packed away, the kidney was placed in a small plastic bag and suspended from a Statham strain gauge transducer GI-8-350 which was connected to a Sanborn 150 recorder.

Blood flows were measured according to the method of Neely and Turner by momentarily occluding the renal vein. The transducer and recorder systems were calibrated in terms of grams. The kidney was weighed by means of the zero suppression of the recorder. With the recorder running and the vein occluded, change in weight of the organ was recorded graphically upon a suitable time base. The slope of a tangent drawn through the origin of this curve is proportional to blood flow.

After control measurements of blood flow had been obtained, the artery, vein, or both were clamped for varying lengths of time. Blood flow was usually measured immediately after the occluding clamps had been removed, 1 hour later, and sometimes 2 hours later. This preparation permitted the measurement of blood flow without introducing the artifacts of cannulation or the necessity of having a properly functioning kidney.

In another series, 10 dogs were prepared as previously described, and control blood flows were measured. These kidneys were

TABLE I.—RENAL BLOOD FLOW (C.C. PER GRAM PER MINUTE) BEFORE AND AFTER OCCLUSION OF RENAL VEIN FOR 30 MINUTES

Dog No.	*Control*	*Immediately after release*	*One hour after release*
6-26-2	1.72	.92	1.54
6-27-1	1.92	1.40	1.36
6-27-2	1.67	2.00	Died
7- 8-1	0.93	0.17	.53
7- 9-1	1.19	1.04	1.96
7- 9-2	1.65	.37	.76
7- 9-3	.76	.92	0
7-10-1	1.75	.80	0
7-10-2	.59	.00	.39
7-10-3	2.28	.81	1.10
Mean	1.45	.84	.85
		(P<.01)	(P<.05)

TABLE II.—KIDNEY WEIGHTS (GRAMS) BEFORE AND AFTER VENOUS OCCLUSION FOR 30 MINUTES

Dog No.	*Control*	*Immediately after occlusion removal*	*One hour after occlusion removal*
6-26-2	68.6	77.9	72.3
6-27-1	50.6	57.2	60.4
7- 8-1	82.3	91.2	82.9
7- 9-1	64.5	74.8	80.5
7-10-2	43.8	48.3	50.2
7-10-3	88.5	98.0	94.8
Mean	66.38	74.57	73.51
		(P<.001)	(P<.025)

TABLE III.—RENAL BLOOD FLOW (C.C. PER GRAM PER MINUTE) BEFORE AND AFTER OCCLUSION OF THE RENAL ARTERY AND VEIN FOR 1 HOUR

Dog. No.	*Control*	*Immediately after release*	*One hour after release*
5- 9-1	.94	.14	0
5- 6-1	2.66	.24	.40
5- 7-1	1.48	.40	.39
5- 7-2	2.66	.59	.96
5- 8-1	1.82	.45	.49
6-20-1	.68	1.24	0
6-23-3	2.44	1.10	.57
6-24-1	.85	.44	.28
6-25-1	3.60	.46	.97
6-25-2	1.88	.80	1.17
6-26-1	1.57	.89	.86
Mean	1.87	.61	.56
		(P<.005)	(P<.001)

treated exactly like the others except that no vessels were occluded. Flows were measured 1 hour after the control flow and again 2 hours later. This latter experiment permitted the determination of the effect of the long term procedure itself upon blood flow.

RESULTS

Thirty minute occlusion of renal vein. In Table I are shown the blood flow data from 10 animals whose renal vein was clamped for 30 minutes. The artery remained patent. Reduction in blood flow immediately after release of the occluding clamp was significant with a P value of less than .01. The mean control flow was 1.45 cubic centimeters per gram of kidney. The mean flow immediately after release was .84 cubic centimeter per gram. After 1 hour the flow was .85 cubic centimeter per gram of renal tissue. This latter change was also significant with a P of less than .05.

Weights of only 6 of the kidneys were recorded. The weights of the kidneys of this group are shown in Table II. The mean of the weights increased from 66.38 to 74.57 grams (P< .001). During the remaining hour the mean of the weights decreased to 73.51 grams. This still differed significantly from the control mean (P<.025).

One hour occlusion of renal artery and vein. In Table III are shown the blood flow data from 11 dogs whose renal artery and vein were occluded simultaneously for 1 hour. The mean control flow for this series was 1.87 cubic centimeters per gram of renal tissue. The mean flow immediately after release of the clamp was .61 cubic centimeter per gram (P<.005). The mean flow 1 hour later was .56 cubic centimeter per gram (P<.001).

The kidney weights are shown in Table IV. The kidney weights increased from a control mean of 62.76 grams to a mean 64.71 grams immediately after 1 hour of occlusion. This did not represent a significant increase. However, after 1 hour the organ weight had increased to a mean of 65.75 grams (P>.10).

One hour occlusion of renal artery. In Table V are shown the blood flow data from 10 animals whose renal artery was occluded for 1 hour. The control mean blood flow was 1.66 cubic centimeters per gram of tissue. The mean flow immediately after release was .72 cubic centimeter per gram, a significant decrease (P<.005). However, after 1 hour the mean flow rose to 1.3 cubic centimeters per gram of tissue. This mean did not differ significantly from the control mean (P<.20).

The renal weight changes are given in Table VI. The control mean weight was

70.36 grams. Immediately after release of the occluding clamps the mean weight fell to 67.5 grams, an insignificant decrease. After 1 hour the mean weight was 74.99 grams. This was an insignificant change from control weights.

Control group. Since the effect of time and also of the dissection upon renal blood flow was not known, the control group was deemed necessary. In 10 dogs the means of the 1 hour and the 2 hour flows did not differ significantly from the controls (of the control group). Therefore, the long term procedure itself does not appreciably affect renal blood flow.

DISCUSSION

According to these data, occlusion of the renal vein results in severe temporary impairment of renal blood flow. The surprising result, however, was the marked difference between arterial and arteriovenous occlusion. This occurrence may be due to blood entrapped within the kidney, since this was the only difference between the arterial and arteriovenous occlusions. This theory supports the work of Crowell and of Webb regarding the detrimental effects of formed elements upon the static circulation. It appears that if surgical occlusion of the kidney is contemplated for any length of time, then one should be certain that the vein is left intact and that venous pressure is not elevated. Further studies are in progress using the wash-out technique of Webb and the heparin technique of Crowell to determine whether the decrease in blood flow is due to clotting or sludging of the formed elements or to some other phenomenon. In this connection, Waugh has shown that kidneys which have been perfused with oil and which have been previously heparinized have less resistance to flow than non-heparinized kidneys.

The detrimental effect of venous occlusion was further demonstrated in this present study by the large increase in organ weight after prolonged clamping of the vein. The weights after simultaneous occlusion of the artery and vein gradually increased to a significant level after 1 hour. This finding must indicate some loss of vascular intactness either to formed elements or to plasma and electrolytes. Again, intravascular thrombosis may account for such an occurrence. After arterial occlusion the weight of kidneys did not increase.

The absence of reactive hyperemia was surprising. Hyperemia appears to occur only after relatively short periods of ischemia. As the ischemic period is prolonged, the hyperemic response diminishes until no longer exhibited.

TABLE IV.—KIDNEY WEIGHTS (GRAMS) BEFORE AND AFTER ARTERIOVENOUS OCCLUSION

Dog No.	*Control*	*Immediately after occlusion removal*	*One hour after occlusion removal*
5- 7-1	44.7	42.2	42.0
5- 7-2	35.3	43.5	44.90
5- 8-1	42.6	35.8	43.3
6-23-3	61.6	62.9	65.2
6-24-1	112.9	109.4	110.8
6-25-1	65.0	67.0	69.1
6-25-2	66.6	78.2	72.3
6-26-2	73.4	78.7	78.4
Mean	62.76	64.71	65.75
		(P<.40)	(P>.10)

TABLE V.—KIDNEY BLOOD FLOW (C.C. PER GRAM PER MINUTE) BEFORE AND AFTER OCCLUSION OF THE RENAL ARTERY FOR 1 HOUR

Dog No.	*Control*	*Immediately after release*	*One hour after release*
3-14- 400	1.48	0	0.39
3-13- 500	2.29	.22	1.99
3-22-1000	2.07	2.71	2.24
5-21-1200	2.65	1.29	2.77
6-13- 1	1.98	.76	.63
6-13- 2	2.24	.66	1.28
6-16- 1	1.07	.20	.25
6-23- 1	.84	.31	1.95
6-23- 2	.51	.20	.31
7- 7- 1	1.43	.85	1.14
Mean	1.66	.72	1.3
		(P<.005)	(P<.20)

TABLE VI.—KIDNEY WEIGHTS (GRAMS) BEFORE AND AFTER ARTERIAL OCCLUSION

Dog No.	*Control*	*Immediately after occlusion removal*	*One hour after occlusion removal*
3-14-400	74.8	74.8	76.8
3-13-500	58.8	55.4	58 8
6-13- 1	75.9	64.8	68.9
6-13- 2	65.7	62.0	69.8
6-16- 1	62.7	56.8	62.7
7-23- 1	76.8	78.7	107.6
7-23- 2	68.4	66.1	71.4
7- 7- 1	79.8	81.4	83.9
Mean	70.36	67.5	74.99
		(P 0.1)	(P 0.3)

SUMMARY AND CONCLUSIONS

1. The effects of various types of vascular occlusion on blood flow and kidney weight were studied by a simple method of blood flow measurement.

2. Venous occlusion has a more pronounced effect on subsequent renal blood flow than does arterial occlusion or arteriovenous occlusion.

3. There was a marked difference between arterial and arteriovenous occlusion on blood flow. It is thought that this difference may be due to entrapped blood with subsequent formation of capillary thrombi.

4. If during surgical procedures it becomes necessary to occlude the renal artery, every effort should be made to prevent occlusion of the vein.

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VASCULAR MALFORMATIONS OF THE SPINAL CORD

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In 1948 Epstein, Beller, and Cohen (2) reported a group of 6 vascular malformations of the spinal cord collected from a group of 77 intradural spinal cord lesions operated upon at the Mount Sinai Hospital from 1931 to 1948. In the decade that has elapsed since their report, we have added 10 additional cases from the Mount Sinai Hospital (Table I) and have had the opportunity to observe 1 of the patients, whom they previously reported on, for more than 10 years.

Although vascular anomalies of the brain have been well known for many years, similar disorders of the spinal cord have been largely disregarded or have gone unrecognized. According to Wyburn-Mason, the earliest reference to vascular malformations of the cord was that of Hebold in 1885. Since that time, isolated examples of such lesions have been reported by various observers. In 1929, Globus and Doshay reviewed the problem and reported 4 cases. Turner and Kernohan, in 1941, in an article concerning vascular malformations and vascular tumors involving the spinal cord, reported 18 cases. Several classifications have been suggested. There has been no uniformity of opinion concerning the pathogenesis of these rather uncommon lesions. Among others, two hypotheses have been commonly advanced concerning the origin of these lesions. According to one theory, vascular malformations of the spinal cord have their origin very much in the same way as varicosities of the lower extremities. In other words, they are more or less mechanical in origin and are due to the upright position of man and interference with the free return of venous blood from the spinal canal. The fact that most cases of vascular malformation of the spinal cord occur in the lower dorsal and lumbar regions and that their incidence is much higher in men than in women would seem to lend validity to this theory.

However, the occurrence of some vascular malformations early in life and in the upper dorsal and cervical regions of the spinal cord are good arguments in favor of a congenital origin. The presence of arterial blood, of course, would preclude the first theory, and in many instances these lesions closely resemble those found within the intracranial chamber.

It is customary to classify vascular malformations into a predominantly arterial, arteriovenous, or venous pattern. However, as spinal anomalies are seldom studied by angiography and minimally handled at operation for fear of increasing cord damage, their structure is even less well understood than their intracranial counterparts. Marked tortuosity and dilatation of the spinal cord vessels adjacent to, and especially below, a tumor are well known to neurologic surgeons. Such alterations secondary to obstruction of the spinal canal must not be confused with vascular malformations which more often than not exist in the presence of a freely open spinal canal.

The clinical features of spinal cord vascular malformations are of considerable interest. In our group of 10 new cases, 8 were in males. The ages varied from 15 to 65 years; the average age being 53.5 years. In 3 patients the onset of symptoms was rather abrupt. In the others, there was a gradual development. Pain was present to a greater or lesser degree in nearly every patient. However, difficulty in the use of the lower extremities was usually the first, or a very early, symptom. This was often associated with low back pain. The symptoms in some patients developed over a period of many years and appeared to be no different than

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TABLE I.—SUMMARY OF CASES

Case *Sex* *Age*	*Onset*	*Pain*	*Lower ext. weakness*	*Sensation*	*Block*	*Protein*	*Myelogram*	*Laminectomy*	*Findings*	*Result*
1 M 65	Gradual	2+	3+	Level T12	0	58	Tortuous defects T9-T12	T8-L1	Large wormlike vessels dorsal surface of cord	Sl. subj. imp.
2 M 58	Gradual	1+	2+	Level T6	0	80	Small circular defects	L1-L5	Paget's disease, small wormlike arterial vessels	Improved
3 M 60	Gradual	2+	1+	Level T8	0	80	Corkscrew-like defects	T10-L1	One large vessel, S shaped curve	Improved
4 M 15	Sudden	+	3+	Normal	0	184	Irregular branching defects	T12-L2	Purplish-red tangle of coiled up vessels	Unchanged
5 M 54	Gradual	+	2+	Level T7	0	72	Irregular serrated column	T7-T9	Arachnoid thickened, beneath it extensive coil thick walled red vessels	Sl. improved
6 F 55	Gradual	2+	3+	Level S3	?	?	Irregular margins of column	T12-L4	Large varices covering cord and roots	Sl. improved
7 M 65	Sudden	3+	4+	Level L3	Complete	Yellow clotting	Bizarre distribution and irregular defect in lower lumbar canal	L2-L5	Arachnoid discolored and thickened, nerve roots bound together, 2 large thrombosed vessels, many small vessels intermingled with roots	Died
8 F 41	Sudden	Backache sev. yrs.	4+	Level T11	0	41	Defects suggesting vascular malformation	T7-T12	Abnormal vessel extending entire length of exposure, second vessel made a loop with this one, appeared thrombosed	Sl. improved
9 M 64	Gradual	2+	2+	Level T10	0	85	Serpiginous defects	T9-T12	Large vascular anomaly, mostly at C7-T1	Sl. improved
10 M 58	Gradual	1+	2+	Level T4 on rt.	Complete	330	Irregular block at T4	C7-T3	Tortuous tangle of large vessels	Worse
11* F 39	Gradual	3+	1+	Level T10	? Almost complete	38	Partial block T12— curvilinear shadows	T10-T12	Tortuous coils and loops of large vessels filled with red blood	Improved

*Previously reported by Epstein, Beller, and Cohen (2).

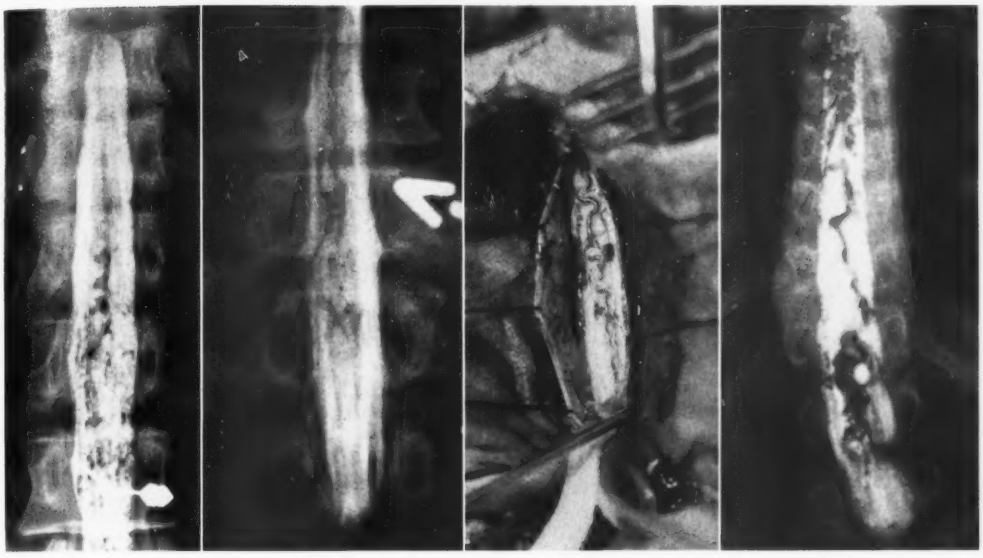

FIG. 1. FIG. 2. FIG. 3. FIG. 4.

FIG. 1. Case 2. Myelogram (pantopaque). Small circular defects. At operation the malformation consisted of a tangle of wormlike vessels containing arterial blood.

FIG. 2. Case 3. Myelogram (pantopaque). Vascular malformation beginning at the level of the twelfth thoracic segment and extending cephalad.

FIG. 3. Case 3. Photograph taken during operation.

FIG. 4. Case 4. Myelogram (pantopaque). At operation a purplish-red tangle of vessels coiled up in a mass about 4 centimeters long and 1.5 centimeters wide was found.

the common type of low back pain often diagnosed as lumbago or sacroiliac disease. In some of the patients, bladder and rectal disturbances developed, leading to incontinence by the time they were admitted to the hospital. No patient had a history suggestive of subarachnoid hemorrhage. On neurologic examination every patient had weakness in the lower extremities. In some, this had progressed almost to complete paralysis so that the patients were bedridden. Every patient, except 1, had sensory disturbances. In 5, the sensory level was in the mid or low thoracic region. One patient had a level at the fourth thoracic segment on the right side, another had a level at the third lumbar and another at the third sacral segment. The youngest patient, a boy of 15, had no sensory changes. On lumbar puncture there was no evidence of bleeding. An open manometric system was found in 7 patients, a complete block in 2, and in 1, the record is not entirely clear. The protein in the spinal fluid varied from 41 to 330 milligrams per cent. In 1 patient the fluid was deeply xanthochromic and clotted almost immediately so that a protein estimate was not made. Myelography was carried out in every patient. In 7, the myelographic appearance in retrospect was quite characteristic of a vascular malformation of the spinal cord. In several patients such a diagnosis was suspected from the myelogram preoperatively even before we realized that a fairly characteristic myelographic pattern could be defined. The defects in the myelogram were described as tortuous, circular, corkscrew-like, irregular, branching, serpiginous, and bizarre. After studying the myelographic picture carefully and comparing the films obtained with those from patients with adhesive arachnoiditis, the differentiation is usually possible, though at times difficult. In arachnoiditis, the opaque ma-

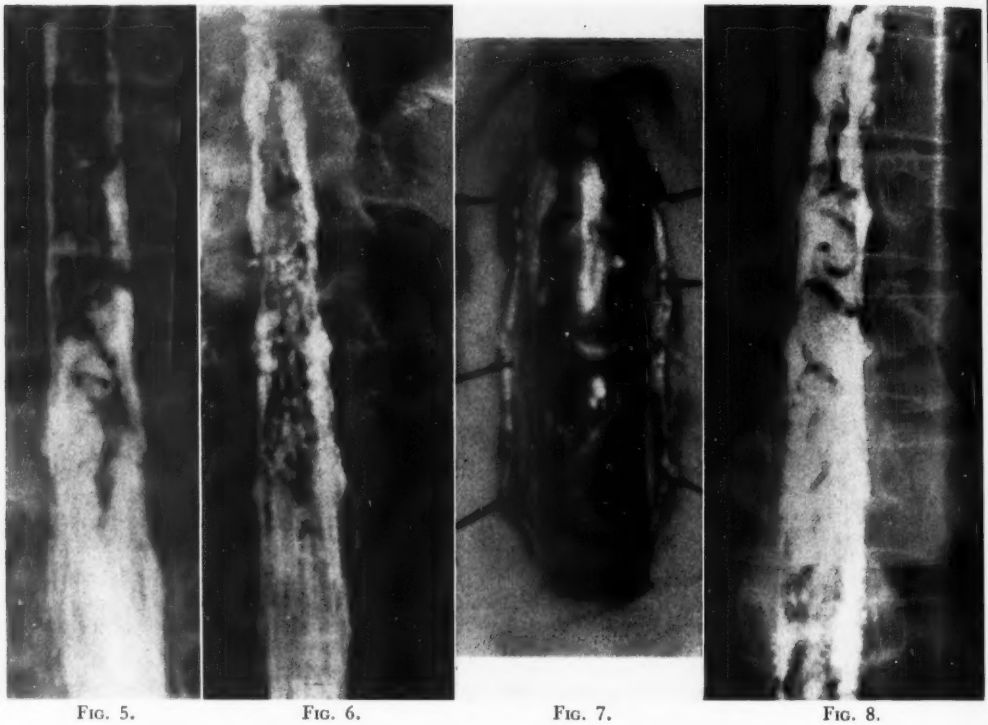

FIG. 5. FIG. 6. FIG. 7. FIG. 8.

FIG. 5. Case 5. Myelogram (pantopaque). At operation coil of thick walled blood vessels containing arterial blood was found.

FIG. 6. Case 9. Myelogram (pantopaque).

FIG. 7. Case 9. Operative photograph.

FIG. 8. Recent case (of M. B. Bender). Man, aged 58 years, sudden onset of severe pain in both buttocks. Pain increased. Six months later paraplegia developed with sensory level at the level of the twelfth thoracic segment. Lumbar puncture showed open manometrics. Myelogram typical of vascular malformation. Operation not advised.

terial is arrested in an irregular, structureless manner. Pantopaque may be scattered in small globules over a large part of the spinal subarachnoid space. As pointed out by B. Epstein (1), the sinuous, smooth walled, channel-like structures of vascular malformations are rarely simulated by the more diffuse changes of arachnoiditis. The myelographic findings in spinal cord tumors, whether extradural, intradural, or intramedullary, are so characteristic that the differential diagnosis between vascular malformations and tumors should rarely cause trouble except when a complete block is present (Case 7). The major purpose served by myelography in these cases is to outline, as negative shadows, the large afferent arterial and efferent venous channels of the malformation, as they bridge the subarachnoid space, and run along the surface of the spinal cord. It is quite likely that, unless full column technique is used where feasible or the region in question is studied with the pantopaque dependent in several positions, vessels entering and leaving the subarachnoid space on one side of the spinal cord may be missed. It is also reasonable to suppose that smaller malformations may be completely missed by this relatively crude technique. Certainly, the development of a safe means of arteriography will add as much to the diagnosis of these lesions as it presently

FIG. 9.

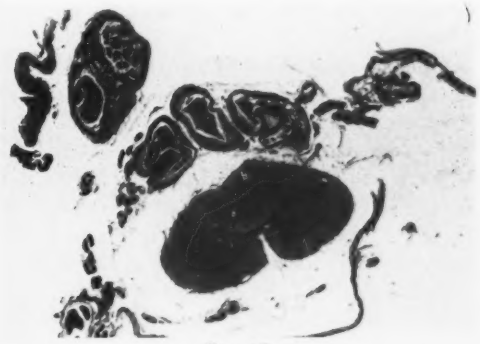

FIG. 10.

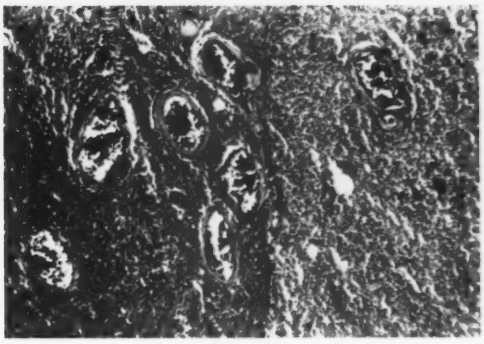

FIG. 11.

FIG. 9. Case 7. Postmortem specimen. Note tangle of vessels on the dorsal surface of thoracic cord and continuing along one of the upper lumbar roots.

FIG. 10. Case 7. Section showing thoracic spinal cord and thick walled vessels of malformation.

FIG. 11. Case 7. Photomicrograph. Thoracic cord showing clusters of hyaline vessels at the base of the anterior horn.

does to cerebral vascular malformations. Recently, a technique has been described for the angiographic visualization of those lesions in the upper cervical region.

The treatment of vascular malformations of the spinal cord on the whole has been relatively unsatisfactory with only an occasional good result. In the present group of 10 patients who had laminectomies, 2 were classed as improved at the time of discharge from the hospital, 5 slightly improved, 1 unchanged, 1 worse, and 1 died. In this series, laminectomy was done in every case since the diagnosis was rarely established beyond doubt from the clinical and x-ray studies alone. At operation no attempt was made to remove or coagulate the abnormal vessels, since in each case there appeared to be an intimate communication between the vessels of the malformation and those of the cord. It was feared that disturbing the circulation in the malformation would interfere with the blood supply of the spinal cord. The dura was left open for decompressive purposes in 4 cases. It was closed in 3. In 3 a fascial graft was used to complete the dural closure so as to allow additional room in the dural sac. In 1 case the operative note is not clear as to whether the dura was closed or not. High voltage x-ray therapy was used in 1 patient. It did not influence the course of the disease.

The pathologic changes in vascular malformations have been fairly consistent in the cases studied at operation or autopsy. The process nearly always involves the lower part

of the spinal cord and has rarely extended above the fifth thoracic segment. Only 1 of our cases was an exception. In Case 10, the abnormality was found from the level of the seventh cervical to the third thoracic segment. In each instance the malformation was encountered on the dorsal surface of the cord often forming a tangle of intermingling vessels resembling a bag of worms. In some patients, these surface vessels contained dark blood. In others, the blood was purple, and in still others it was described as red. Obviously, the color of the lesion depended on whether it was predominantly venous or arterial in origin. In several the adjacent arachnoid was thickened and specimens removed at surgery for biopsy showed infiltration with inflammatory cells. One of our patients (Case 7) presented himself with a sudden onset of complete motor and sensory paralysis below the level of the third lumbar segment and died of a severe pneumonia on the third postoperative day. Autopsy showed severe acute suppurative bronchopneumonia, esophagitis, and acute gastritis with ulceration and hemorrhage as well as the vascular malformation of the spinal cord which was found at surgery (Fig. 9). Large sinous vascular channels were present on the dorsal surface of the cord extending from the cauda equina to the lumbar enlargement. On microscopic study these showed marked intimal and adventitial fibrosis of the vessel walls. Large thin walled veins extended into the posterior roots which were the seat of fibrosis and degeneration in the region of the abnormal veins. Large thick walled veins were also found on the ventral surface of the cord and in the anterior fissure. The lower dorsal cord, on section, showed clusters of large hyaline vessels at the base of the anterior horns. Myelin stain showed small areas of loss of myelin sheaths and swelling of the axis cylinders in the lateral and anterior tracts.

SUMMARY AND CONCLUSIONS

Our review of vascular malformations of the spinal cord leads to these conclusions:

1. The disease is found mainly in middle aged or elderly males.

2. There is usually a long history of low back pain often going on for many years.

3. Weakness in the lower extremities along with subjective and objective sensory changes may develop slowly and lead to neurologic investigation. Upper extremity involvement was not found in any of these cases.

4. The sudden onset of a complete or almost complete transverse cord lesion occurs in some patients, 3 out of 10 in the present group. This is possibly related to thrombosis of vessels in the malformation and in the cord.

5. Lumbar puncture most often yields a clear fluid with normal dynamics although manometric block is found occasionally. Two out of 10 had a complete block and 1 an almost complete block in this series.

6. An accurate preoperative diagnosis can be made in most cases by pantopaque myelography.

7. The results of surgical treatment have been generally disappointing. However, we have observed 1 patient (Case 11) who had an excellent result for more than 10 years. This case was previously reported by Epstein, Beller and Cohen (2). She had an almost complete block prior to surgical intervention. Laminectomy was followed by marked improvement and this has been maintained for more than 10 years.

8. Laminectomy is probably indicated only in those patients who have a complete block on manometric study or myelography.

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HYSTEROSALPINGOGRAPHY WITH A NEW WATER-SOLUBLE MEDIUM (SINOGRAFIN)

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HYSTEROSALPINGOGRAPHY is universally used in diagnostic problems related to the female pelvic organs. In some instances, it has been proved to be helpful in the treatment of sterility. Early attempts, however, to study the uterus and oviducts roentgenographically were not particularly successful because the contrast agents employed were too irritating to the patient or gave poor delineation. In 1924, Heuser, in Argentina (3, 4) and Portret in France introduced iodized oil for uterotubography and the following year Béclère began his studies of sterility and pelvic tumors, using iodized oil as the contrast medium. The new medium was found to avoid the difficulties of irritation which had been encountered with earlier media, and to provide good contrast. Interest in hysterosalpingography was promptly revived. Iodized oil has been widely and successfully used over the past decade to outline the uterus and tubes, with only rare reports of complications. The hazard has remained, however, of oil peritonitis from unabsorbed oil in the peritoneal cavity or embolism from accidental intravasation of the medium. Moreover, the risk of reactivating dormant pelvic infection has appeared to be higher with oily media.

Water soluble media designed to obviate the problems associated with oily media have generally proved not to be satisfactory because of poor technical results or, in some cases, because of difficulty from ingredients —usually carboxymethyl cellulose—added to increase viscosity. In 1955, Erbslöh, in Germany, reported that a new water-soluble medium identified as endografin possessed viscosity ideal for hysterosalpingographic examination without additives. In subsequent reports, endografin was found to be satisfactory in a number of cases but in others pain and peritoneal irritation occurred.

A new contrast medium, designated as sinografin, was recently introduced for use in hysterosalpingographic examinations. This medium has been employed in selected cases at this center since June 1957 with exceptionally satisfactory results. Experience with sinografin in the department of radiology of this large city hospital as well as in a private office is briefly described in this communication.

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MATERIALS AND METHODS

The contrast agent. Sinografin is an aqueous solution of the methylglucamine salts of diatrizoate and iodipamide. Diatrizoate is present (as the acid) in 40 per cent concentration, iodipamide (as the acid) in 20 per cent concentration. The formulation as supplied contains approximately 38 per cent iodine. The preparation has a viscosity of 29.8 centipoises at 250 C. No viscosity additives are present.

Each of the components of sinografin has been shown, when used separately, to be an effective and safe radiopaque medium. Diatrizoate methylglucamine[1] has been successfully employed in intravenous urography, in cerebral angiography, and in aortography. In comparative studies, the incidence of untoward reactions following the intravenous administration of diatrizoate methylglucamine was lower than that with several other widely used contrast agents. Iodipamide methylglucamine[2] has

[1]Renografin, 60 per cent, 76 per cent, or 30 per cent.
[2]Cholografin methylglucamine, 52 per cent.

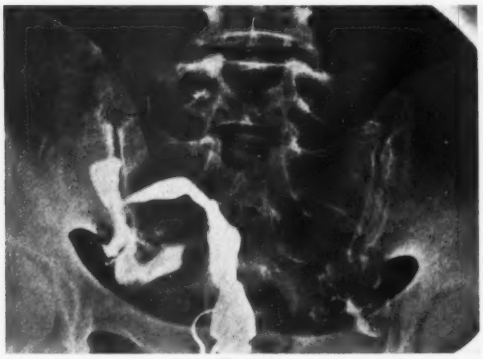

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 1. Sterility problem for 4 years. Elongated cervical canal is demonstrated with uterus of the infantile type deviated to the right. The right tube is dilated. The left tube is normal.

FIG. 2. Sterility problem. Rubin test was equivocal. Uterine cavity is normal and both tubes are patent. Ten cubic centimeters of sinografin were used.

FIG. 3. Patient complained of irregular bleeding for several months. Two Aschheim-Zondek tests were negative. Irregular filling defects demonstrated with sinografin in uterine cavity which is slightly enlarged. Two weeks after examination patient had a miscarriage.

been employed extensively in intravenous cholangiography and cholecystography with resulting excellent contrast, without serious reactions. A combination of both of the components of sinografin in a single preparation (duografin) has also been successfully used intravenously.

The successful and extensive intravenous use of both of these components of sinografin, either separately or combined, denotes the safety of this preparation for intrauterine injection, even though some of the material may inadvertently enter the blood stream by accidental intravasation.

The patients. During the period from April 1957 to August 1958, a total of 50 patients was referred to the department of radiology, and to a private office, for hysterosalpingographic examination. Of these 50 patients, 32 presented evidence of sterility, the remaining 18 showed signs and symptoms of other disorders pertaining to the female pelvic organs. Two patients had undergone recent surgery.

Technique. Total dosage of sinografin ranged from 5 to 10 cubic centimeters, the usual dose being 10 cubic centimeters. In all cases, sterile precautions were used. The vaginal canal and cervix were cleaned with either zephiran or merthiolate. A sound was placed in the cervix in order to determine the position of the uterus. A tenaculum was then applied to the cervix and a cannula inserted into the cervical canal. In cases in which uterine disease was suspected, routine serial studies were made

FIG. 4.

FIG. 4. Sterility problem. Excellent hysterosalpingogram with sinografin shows normal filling of uterus and tubes.

FIG. 5.

FIG. 5. Extrauterine pregnancy was suspected in this case. Hysterogram was obtained with sinografin to confirm the diagnosis. Sinografin is apparent in the uterus in the pelvis. The uterine cavity shows normal filling. The fetus is in the abdomen adjacent to uterus.

following the injection of 0.5, 1, 2, and 3 cubic centimeters of sinografin. Each film was developed immediately after exposure and if any pathologic condition was suspected from the wet films, additional films were exposed, using more of the dye. When indicated, a lateral film was made with the instruments in situ. Constant tension applied to the tenaculum and cannula yielded better results.

In cases in which tubal disease was suspected or sterility was the problem, the procedure was the same except that injections began with 1 cubic centimeter of sinografin and, if it was possible, the entire 10 cubic centimeter dose was administered.

The serial films were developed immediately and inspected in the dark room in order to determine the number and type of films required.

Each patient was questioned as to whether she felt pain or discomfort during and after the examination.

RESULTS

The films were entirely satisfactory in every case except 1. The quality of contrast was considered to be excellent in 42 cases, and good in 7. Representative films appear in Figures 1 to 4. Poor results in a single instance were not attributable to the medium but rather to the fact that the patient had a small cervical os and the medium spilled into the vagina instead of proceeding into the uterine cavity.

Conditions present in the patients which were demonstrated in the films are tabulated as follows: in 32 patients with sterility, tubal patency in 25, tubal occlusion in 6, and intrauterine defect in 1; in 18 patients with other disorders, intrauterine defect in 4, abnormally small or large uterine cavity in 2, juvenile-type uterus in 1, uterine or cervical polyps in 3, intrauterine fibroid in 1, retroverted uterus in 1, intra-abdominal pregnancy in 1 (confirmed at operation), possible intra-abdominal pregnancy in 1, normal filling of uterus and tubes in 3,

and small cervical os in 1. The demonstration of intra-abdominal pregnancy in 1 case was particularly well defined (Fig. 5).

There were no reactions to the medium in the entire series and no complaints of pain. Two patients complained of slight abdominal cramps lasting for from 10 minutes to 1 hour after the examination. In 1 of these cases, intra-abdominal pregnancy was present.

DISCUSSION

The consistently good or excellent films obtained in this study with sinografin, without reactions, support the conclusion that it is a superior contrast agent for use in uterotubography. The contrast density and viscosity of the preparation appear to be well suited for this purpose. Following its injection into the uterus, the medium readily flows from the uterus into the tubes, outlining both the uterine and tubal cavities satisfactorily within a matter of seconds. There were no complaints of pain in this series despite the use of excessive amounts of dye in many cases in order to attempt to bring on symptoms of cramps or pain. The combination of definitive contrast without unpleasant sequelae provided by sinografin is indeed gratifying and indicates that the agent would be suitable for routine use in any diagnostic problem in which hysterosalpingographic studies would be desirable.

SUMMARY

Sinografin, a new water-soluble contrast agent, has been employed in hysterosalpingographic studies in 50 patients, 32 of whom presented problems of sterility and the remaining 18 signs or symptoms of other disorders referable to the female genital organs or related pelvis. Good or excellent films were obtained in every case save one in which the poor results were not attributable to the dye. There were no untoward reactions and no pain following examination with sinografin. Two patients complained of slight cramps.

On the basis of the results obtained in this study, it is concluded that sinografin is a superior contrast agent, suitable for routine use in hysterosalpingography.

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THE USE OF ISOLATED LOOPS OF BOWELS IN UROLOGIC SURGERY

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THE HISTORY of urinary diversion has been characterized by three rather specific periods in urologic endeavor stimulated by the problems most needing resolution at that time: (1) the surgical phase, (2) the renal phase, and (3) the electrolyte phase. The first stage was characterized by the attempt of surgeons to perform urinary diversion to meet the needs of the organism in relation to other disease. The earliest known of these attempts in modern times was recorded by John Simon in a case of exstrophy of the bladder using the technique of fistula formation with a silk thread. Thomas Smith performed the first ureteral transplantation into the bowel in man in 1878 using a direct axial transplantation. This principle now revised and revived in recent years in ureteral ileal transplantation is the basis of our modern technique although others have claimed the originality of this procedure. Since the time that Pawlik performed his first total cystectomy in 1889 and Martin in the United States in 1899 for carcinoma of the bladder, multiple surgical techniques have been devised in an attempt to make the procedure surgically feasible, decrease mortality and morbidity, and combat the problem of the combination of the urinary and the fecal stream. Hinman in 1936 in his excellent review of the literature up to that time reported that 60 different surgical techniques by 50 surgeons had been attempted.

The feasibility of performing ureteral intestinal anastomosis having been demonstrated, the second phase of this endeavor is characterized by operations devised to protect the renal function of the individual by methods of anastomosis which would prevent back pressure and pyelonephritis. Perhaps the most significant contribution in this direction was that of Coffey in 1910 whose procedures, designated Coffey No. 1, 2, and 3, dominated the field of ureteral intestinal anastomosis for many years. The literature contains many modifications of these techniques which attempt to prevent reflux and chronic infection of the upper urinary tract as well as to obviate the calamities of ureteral intestinal anastomosis, such as sloughing and stenosis at the suture line. Nesbit, Jewett, and Flocks, and later Cordonnier and Leadbetter, contributed to this problem.

Due to the appreciation of electrolytes and renal function since the second World War, impetus for the third stage in the fight for the solution of these problems crystallized with an end-to-side anastomosis of the ureter in an isolated ileal loop. With the realization that, irrespective of our surgical techniques or abilities, the basic problem resolved itself to one of renal physiology and electrolyte balance, diversion of the urinary stream from that of the fecal stream became uppermost in the minds of the individuals interested in this problem. While it is true that the first substitution for the urinary bladder was made by Tizzoni and Foggi in 1888 in dogs with the use of an isolated piece of ileum and was followed by the French and German surgeons, Heitz-Boyer and Hovelacque as well as Cuneo and Marion and Kotzenberg, it was not with an appreciation of the problem at hand at the present that these procedures were devised. Nor at the time in 1943 when Bisgard experimenting in dogs using a piece of

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FIG. 1. Case 2. Preoperative intravenous pyelogram showing the distortion of the bladder due to the tumor and minimal obstruction of the left ureter.

FIG. 2. Case 2. Postoperative intravenous pyelogram revealing fine delicate ureters and calyces with excellent drainage.

isolated sigmoid for the urinary bladder, nor Rubin when he reported in 1948 his experiences with the sigmoid as a substitute for the urinary bladder; nor when I reported my own observations on isolated sigmoid loop substitution following total cystectomy in the dog in 1950, were we quite aware of the physiologic implications of the procedure then being investigated.

It is obvious from a perusal of the literature at the present time that there is unanimous agreement that separation of the urinary and fecal stream is pertinent to long term survival, as well as reasonable normalcy of the renal mechanism and electrolyte balance. The works of Baum, Gross, Pyrah, Cordonnier, Campbell, Bricker, Amos, and others all substantiate the feasibility of the use of an isolated piece of ileum as a urinary conduit with maintenance of normal renal physiology and electrolyte balance. This anatomic substitution has found its place in urology both as an artificial conduit for the urine in place of the bladder, as a conduit for the urine in place of the ureter, and as an additive factor in the reservoir function of the bladder. It is desired to report our experiences with this problem as well as to report the first case of total replacement of the ureter in a child with a single kidney.

CASE 1. F. A., 17 year old female, was admitted to the hospital on April 11, 1954 with a diagnosis of myelomeningocele with urinary and fecal incontinence since birth. The patient, a small, fairly well developed female from the waist up, who had bilateral atrophy of both legs and who used crutches for mobilization had been incontinent of urine and feces since birth. Fecal incontinence was controlled by constipation and enemas every second or third day. Multiple procedures to correct the urinary incontinence had previously been unsuccessful. She had suffered repeated attacks of pyelonephritis. On April 16 1954 resection of the sigmoid was carried out with isolation of a loop of sigmoid, end-to-end anastomosis and reconstitution of the fecal stream. The isolated

FIG. 3. Case 4. Preoperative intravenous pyelogram of the single right kidney showing the mass of hydronephrosis.

FIG. 4. Case 4. Intravenous pyelogram taken 10 days postoperatively after formation of ureter from isolated ileal loop. Hydronephrosis is more extensive at this time.

loop was brought out as a urinary colostomy, and bilateral ureteral intestinal anastomosis was carried out. Results of the preoperative and postoperative chemical examinations were negative. The postoperative course was complicated by an attack of pyelonephritis which responded well to antibiotic therapy. She was discharged on the twentieth postoperative day with a catheter in place draining the urinary colostomy. She did well except for recurrent bouts of pyelonephritis. On November 28, 1955, a right nephrectomy was carried out because of severe hydronephrosis and pyelonephritis on the right side. Since that time for a period of 4 years she had been completely asymptomatic. The intravenous pyelograms demonstrate function essentially within normal limits and the electrolyte pattern is within normal range. She wears an ileostomy bag and maintains an adequate urinary toilet without difficulty. She is asymptomatic from a urinary standpoint.

CASE 2. G. C., a 56 year old male, was admitted to the hospital on May 21, 1957 with a diagnosis of carcinoma of the prostate. Cystoscopy and transurethral resection of the lesion revealed a transitional cell carcinoma of the bladder and an adenocarcinoma of the prostate (Fig. 1). On June 13, 1957 a total cystostomy with prostatectomy and seminal vesiculectomy was carried out. Formation of an ileal loop bladder and bilateral ureteral ileal anastomosis was achieved. The patient's postoperative course was entirely benign. The gastric tube was removed on the third postoperative day, and by the fourth postoperative day he was having normal bowel movements. He was up and walking from the first postoperative day. Results of preoperative and postoperative chemical examinations were negative. He is now wearing an ileostomy bag without any difficulty with his urinary toilet (Fig. 2).

CASE 3. P. S., a 66 year old male, was admitted to the hospital on July 30, 1957 with a diagnosis of carcinoma of the bladder. This was a large papillary carcinoma involving the trigone and the region of both ureteral orifices with multicentric origin. On August 5, 1957 a total cystectomy with prostatectomy and seminal vesiculectomy was performed, and portions of the terminal ureter were resected as well as the appendix. An ileal loop bladder with bilateral ureteral intestinal anastomosis was constructed. His postoperative course was complicated with intermittent obstruction. On the tenth post-

FIG. 5. Case 4. An intravenous pyelogram taken 6 months postoperatively showing marked reduction of hydronephrosis.

operative day exploration was carried out, and release of bands of adhesions was successful in relieving this intermittent small bowel obstruction. Subsequently, his postoperative course was uncomplicated. Results of preoperative and postoperative chemical examinations were negative. Since that time this man has been entirely asymptomatic from the urinary standpoint. He wears an ileostomy bag and maintains an adequate urinary toilet. He was discharged home on the thirty-third postoperative day. He has had 1 attack of small bowel obstruction which was relieved by conservative therapy.

CASE 4. W. C., an 8 year old male, was admitted to the hospital on September 22, 1957 with a diagnosis of right hydronephrosis, right nephrostomy, and absence of left kidney. This patient had undergone multiple urologic procedures since the age of 2 years at which time a severe obstruction of the vesical neck was noted. Bilateral hydronephrosis and hydroureter were present with extensive obstruction of both kidneys. The left kidney had been removed because of a pyonephrosis. Resection of the vesical neck had been carried out, but secondary obstruction of the ureter due to tortuosity and kinking had resulted in increasing hydronephrosis. Attempts to reconstruct the ureter had been unsuccessful and the patient was wearing a nephrostomy tube at the time of admission (Fig. 3). On September 26, 1957 an isolated loop of ileum was anastomosed to the bladder and to the renal pelvis in the right gutter after mobilization of the entire cecum and ascending colon. The ileal loop was passed through the mesentery of the ascending colon and the ascending colon had then been replaced over the ileal loop. The fecal stream was reconstituted by end-to-end anastomosis. The postoperative course was entirely benign. The gastric tube was out on the fourth postoperative day and he was taking a full diet by the fifth postoperative day. The nephrostomy tube was removed on the seventh postoperative day and the wound dried up immediately. On the ninth postoperative day the urethral catheter was removed and he voided well with good control. He was discharged home on the tenth postoperative day (Fig. 4). Results of preoperative and postoperative chemical examinations were negative (Fig. 5).

CASE 5. E. D., a 39 year old female, was admitted to the hospital on September 23, 1957 with a diagnosis of myelomeningocele, hydrocephalous, urinary incontinence, and sigmoid colostomy. This patient had had urinary and fecal incontinence since birth. Several years before a sigmoid colostomy had been carried out to control the fecal incontinence. At the time of admission, she was wearing a No. 40 Foley catheter but was still incontinent about this. There were large ulcerations of the buttocks with diffuse cavitation extending up toward both ischiatic tuberosities, and osteomyeolitis was present. An intravenous pyelogram revealed a nonfunctioning kidney on the left side and chronic pyelonephritis on the right (Fig. 6). On September 28, 1957 formation of an ileal loop bladder was carried out with ureteral ileal anastomosis. The postoperative course was complicated. Renal shutdown with hyponatremia occurred for the first 3 days. This was treated with 5 per cent sodium chloride intravenously. On the third postoperative day, urinary excretion occurred and increased to normal limits. She did extremely well and was out of bed in a wheel chair taking a normal diet and was afebrile. The ileal bladder worked well with adequate urinary excretion and normal blood electrolytes. On October 5, 1957 the blood urea nitrogen was 10; sodium, 140; potassium 3.9; carbon dioxide combining power, 24; and chlorides, 104 milliequivalents. Evisceration occurred on the ninth postoperative day in spite of the fact that through-and-through retention sutures had been placed at the time of operation. The dehiscence was closed and the patient again responded well so that 3 days following the dehiscence she was taking fluid by mouth with normal bowel function and urinary excretion. On the evening of twelfth postoperative day she went into shock, cardiac failure supervened and pulmonary edema

occurred. All attempts to combat this condition failed, and she died on the fifteenth postoperative day. Autopsy revealed an atrophic, small, chronically pyelonephritic left kidney and an essentially normal sized right kidney with chronic pyelonephritis. Both ureters were essentially within normal limits. The ureteral and intestinal anastomosis was intact and the ileal loop appeared to be well formed and to be functioning satisfactorily. There was no evidence of leaking at the suture lines.

CASE 6. M. M., a 73 year old female, was admitted to the hospital on July 30, 1957 with a diagnosis of carcinoma of the bladder. Cystoscopic examination of this patient revealed a large multicentric diffuse infiltrating carcinoma of the bladder involving the trigonal area and vesical neck. On August 6, 1957 an ileal loop bladder was formed as the first stage of a two stage procedure. The patient tolerated the procedure well but on the first morning postoperatively it was noted that she had physical findings consistent with a left hemiplegia. Results of preoperative and postoperative chemical examinations are depicted in Figures 7 and 8. During her entire postoperative phase she presented a problem of electrolyte imbalance with a low sodium and a low carbon dioxide combining power and a relatively high chloride consistent with a diagnosis of hyperchloremic acidosis. She responded well enough so that on August 29, 1957 a total cystectomy was carried out. For the first few weeks postoperatively her course was reasonably satisfactory though she continued to present problems of renal function and electrolyte imbalance. Subsequently, she suffered several minor cerebral episodes with gradual deterioration. A wound abscess developed, and her course was progressively downhill until she died on October 7, 1957, forty days after the total cystectomy. Autopsy revealed essentially normal appearing kidneys, but, on the left side, evidence of pyelonephritis was present. There was no evidence of obstruction. Both ureters appeared essentially within normal limits. There was no dilatation. Both ureterointestinal anastomoses were intact and apparently functioning normally. Interestingly, the ileal loop was found to be about twice the size needed for the usual length as a conduit with a redundant portion proximal to the left ureterointestinal anastomosis.

CASE 7. W. R., a 75 year old white male, was admitted to the hospital on February 1, 1958 with a diagnosis of carcinoma of the bladder. Cystoscopic examination revealed a large fungating tumor involving the entire base of the bladder and the area of both ureteral orifices. An intravenous pyelogram revealed no function on the right side and a trace of function on the left in 40 minutes (Fig. 9). Laboratory findings were: blood urea nitrogen, 19; hemoglobin, 12.6 grams; hematocrit, 36; white blood count, 6,400. On February 2, 1958 a right ureterostomy and on February 5, 1958 a left ureterostomy were performed.

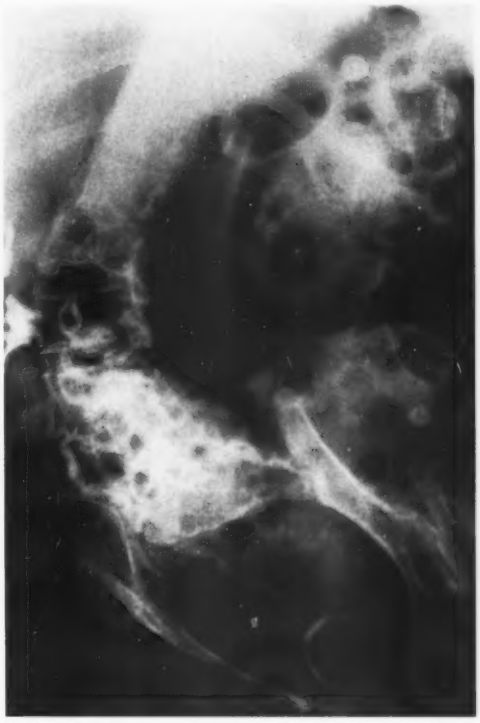

FIG. 6. Case 5. Preoperative intravenous pyelogram showing a fairly normally functioning right kidney with marked twisting and kinking of the right ureter. The left kidney was functionless by this examination. The bladder can be seen as a small ring of dye about the large No. 40 Foley catheter. The extensive distortion of the vertebrae and pelvis is noted on this film.

Six days later re-evaluation of the bladder tumor was carried out and structed and bilateral ureteral ileal anastomoses were performed. On the sixth day a small dehiscence occurred in the center of the wound about 2 inches in length. This was closed without difficulty. On March 4, 1958 total cystectomy with prostatectomy and seminal vesiculectomy was carried out without difficulty. Three days later an old right inguinal hernia became strangulated necessitating repair.

This patient tolerated all procedures excellently. He was out of bed the following day after each procedure and made continuous improvement from the time that bilateral drainage was established by ureterostomy. Ureterostomy tubes were removed following the formation of the ileal loop bladder. The patient was discharged on March 23, 1958. He was markedly improved. He had an excellent appetite and the ileal bladder was working without difficulty. An intravenous pyelogram on March 21, 1958 revealed an almost normal right kidney and a hydro-

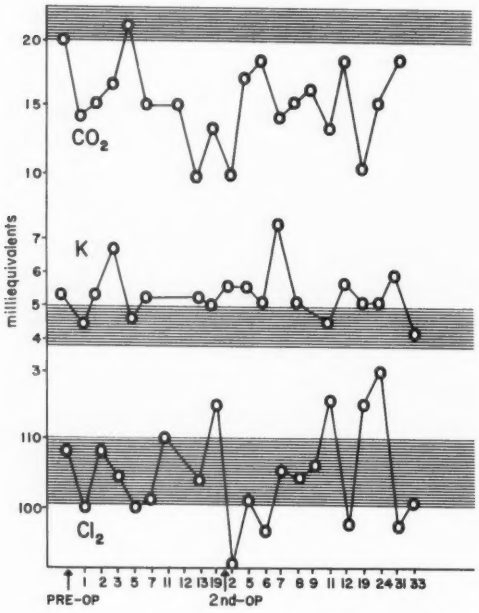

FIG. 7. Case 6. Preoperative and postoperative chemical determinations.

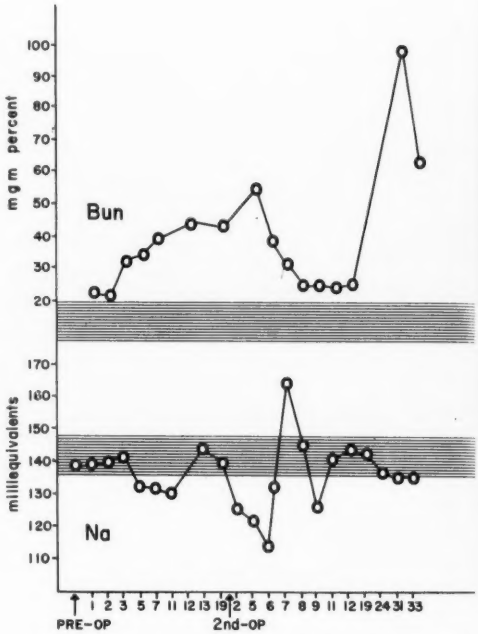

FIG. 8. Case 6. Preoperative and postoperative chemical determinations.

nephrotic left kidney (Fig. 10). There was marked improvement in the concentration of dye which previous to operation failed to reveal itself in 40 minutes. Throughout his entire course results of blood chemistry examinations remained essentially negative.

DISCUSSION

Experiments of a nature unprecedented by protocol have revealed many essential facts in the study of the natural history of a disease process. Serendipity in the laboratory has resulted in unforeseen problems and their eventual solution. Case 6, while unplanned and not preceded by any definite idea of experimentation more than the usual hoped for good end result of a surgical procedure, has provided us with a much needed clinical experiment and experience. In this individual with an ileal loop almost twice as long as necessary, hyperchloremic acidosis and elevation of the blood urea nitrogen were a consistent finding throughout her course. Hyperkalemia of mild degree was persistent. Bricker reporting on 118 pelvic exenterations and 33 other cases of ileal bladder substitution failed to note the presence of hyperchloremic acidosis. Cordonnier in 41 patients found the incidence to be zero. Kusunoki had 1 patient in 13 individuals with ileal bladders who showed evidence of hyperchloremic acidosis. Stamey and Scott in 14 patients found no evidence of this tendency. The latter authors theorized on the possibility of making the ileal loop bladder longer than advocated and doubted if it would result in any disturbance of the electrolyte pattern. "It may be that the length of the loop can be safely elongated without greatly altering the magnitude of these absorptive and secretory phenomena."

It is interesting to theorize what would have been done had this patient survived her cerebral vascular accidents. Certainly, cystography would have revealed the unusual and the unnecessary length of the loop. If we had then explored and ampu-

FIG. 9. Case 7. Preoperative intravenous pyelogram demonstrating just a trace of function from the left kidney.

FIG. 10. Case 7. Postoperative intravenous pyelogram taken 5 weeks after the formation of an ileal loop bladder showing excellent function with bilateral hydronephrosis.

tated this redundant portion of the ileal loop, would her hyperchloremic acidosis have resolved and the hyperkalemia reverted to normal? I believe that such events would have occurred and the end result would have been good. Perhaps it is indicated then that whenever hyperchloremic acidosis is noted in an ileal loop bladder, cystography and measurement of the length of the loop should be made with the intent of revision in mind.

Until there are indications to the contrary, it would seem reasonable to assume that: (1) the ileal loop bladder should be kept below 20 centimeters in length; (2) the stoma should be kept open by periodic dilatation and should be of such caliber as to easily admit the finger; (3) the use of a technique of cutting an opening through the abdominal wall as advocated by Scott and Stamey rather than using a stab wound for the ileostomy is imperative; and, (4) in any case of hyperchloremic acidosis cystography should be carried out again and measurement of the loop should be determined with the intention of revision if indicated.

Case 4 is the first instance to be reported in which an isolated loop of ileum has been used to replace an entire ureter in a child with a single kidney. In this case there was a large hydronephrosis with a permanent nephrostomy tube in place. The patient's postoperative course was entirely benign and rather remarkable for the procedure which was performed. He was out of bed walking on the first postoperative day. The gastric tube was removed on the fourth postoperative day, and he was taking a full diet by the fifth. The nephrostomy tube was removed on the seventh day and his wound dried up immediately. On the ninth postoperative day, the urethral catheter was removed, he voided well with good control, and was discharged home on the tenth postoperative day. Ulm reported the first case in an adult in January 1958.

There are several differences in technique which I believe are important and are responsible for the benign postoperative course of this individual. These differences are based upon a critical re-evaluation of urologic practices and procedures and the paradoxes of many present day ideas. The anastomoses of the ileum to both the pelvis and the bladder were carried out with No. 00 atraumatic chromic catgut by using a continuous suture and an inverting Connell stitch in a similar manner as an end-to-end bowel anastomosis. No drains were placed to the site of the anastomosis and no splinting tubes were used. The nephrostomy tube was left in place 7 days and the urethral catheter in the bladder for 9 days. This technique is in marked contrast to the procedures recorded in the literature in which large through-and-through splinting tubes are used through kidney, ileum, and bladder with suprapubic drainage and these appliances are kept in place for long periods of time—from 2 to 3 weeks. In most cases reported in the literature, drains have been used down to the point of anastomosis. In my estimation the use of through-and-through splinting of the ileum is an unnecessary procedure and merely complicates the postoperative care and prolongs the period of hospitalization. The use of drains down to the point of anastomosis prolongs the postoperative course of the patient and acts as a focus of infection and irritation. These procedures are indeed a paradox of urology in the face of the present methods of ureterointestinal anastomosis using through-and-through sutures of No. 0000 atraumatic catgut. If there is no reason for splinting or draining in the latter procedures certainly there can be absolutely no basis for them in the former.

CONCLUSIONS

My experience with the use of isolated loops of bowel in urology are reported.

1. The first case of complete substitution of a ureter in a child with a single kidney has been documented.

2. In the light of our experience and that recorded in the literature, it would seem inadvisable to make the isolated piece of ileum used as the ileal bladder longer than 15 to 20 centimeters.

3. If following the formation of an ileal loop bladder, hyperchloremic acidosis and hyperkalemia are noted, evaluation of the isolated loop in relation to its length should be investigated and revision attempted as indicated.

4. The practice of splinting the ileum when substituted for the ureter is condemned.

5. Anastomosis of ileum to the kidney and bladder should be performed by a technique similar to bowel anastomosis.

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HUMAN BRAIN CHANGES IN CARDIAC ARREST

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MANY CASES of cardiac arrest have been reported previously from a clinical standpoint, but only a few case reports have described the pathologic changes in the nervous system following cardiac arrest. This situation presents an unusual opportunity to study the vulnerability of the brain to varying periods of cerebral anoxia in man and thereby offers more knowledge in evaluating the clinical effects of acute and chronic oxygen deficiencies upon the brain.

The duration of cardiac arrest has been standardized in this report according to the definition of Barber and Madden (1, 2), as the period between the cessation of the heartbeat and the performance of manual cardiac massage, for it has been demonstrated that circulation to the entire body is established the moment cardiac massage is initiated. This period must be clearly defined in order to avoid confusion in the interpretation of the pathologic changes in patients who do not survive the anoxia of cardiac arrest. Reported cases in which the period of cardiac arrest included the time spent in massaging the heart and administering artificial respiration, according to these standards, would be overestimated.

In this presentation, 2 cases of cardiac arrest will be described, and the pathologic changes in the brain will be correlated with the duration of cardiac standstill and the survival period.

CASE REPORTS

CASE 1. O. L., a 35 year old Negro woman, was admitted to the Jefferson Hospital on August 28, 1955 with the chief complaint of pain in the right hip of 18 years' duration.

Although she had suffered from intermittent pains in the right hip for the past few years, the pain had increased in intensity following a recent automobile accident. She entered the hospital for elective surgery after roentgenograms revealed a severe osteoarthritis of the right hip. The general physical examination demonstrated a 1 inch shortening of the right leg, but otherwise the patient appeared to be normal.

Morphine sulfate (gr. ⅙) and atropine sulfate (gr. 1/150) were administered hypodermically 1 hour before the operation. The anesthesia was started with pentothal sodium intravenously and followed by nitrous oxide and anectine. Twenty minutes later, the patient's blood pressure dropped from 130/80 to 80/60 and she experienced some difficulty in breathing which was attributed to laryngospasm. An endotracheal tube was inserted with great difficulty and a suitable airway was not present. When the prosthesis was inserted into the hip joint, cardiac action ceased. The patient was turned upon her back, the left pleural cavity was opened, and cardiac massage was started within 4 minutes. The blood pressure returned to 120/60 10 minutes later and the pulse was full and regular at 90 per minute. A tracheotomy was performed and an oxygen catheter was inserted into the tube. Five hours later, her temperature rose to 104 degrees F. with the pulse being elevated to 118 beats per minute and respirations, 40 per minute. She remained comatose throughout the entire postoperative period and died 27 hours after the episode of cardiac arrest.

Postmortem examination was performed 9 hours after death. A bilateral pneumonitis was found in both lungs as well as atelectasis of both lower lobes. The brain weighed 1,300 grams and many dilated congested vessels were present over both cerebral hemispheres. There was extravasation of blood over the superior surface of both frontal lobes. The meninges, at the base of the brain, appeared to be slightly thickened. There was a slight cerebellar pressure cone and notching of both unci. Coronal sections showed no gross abnormalities.

At microscopic examination blocks of tissue from the brain were stained by hematoxylin-eosin, toluidine blue, and by the Weil myelin sheath method. The leptomeninges showed spotty thickening and congestion of the blood vessels. There was some extravasation of red blood cells in the meninges over the frontal lobe. In the frontal lobe, the cortex had the appearance of diffuse rarefaction with dilated perivascular spaces. There was a loss of neurons which appeared in the third, fourth, and fifth layers (Fig. 1). The remaining neurons had a homogeneous eosinophilic staining of the cytoplasm with hematoxylin-eosin preparation and a powdery pale effect in the Nissl sections.

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Elongated microglia were present throughout the cortex. Astrocytes with pale nuclei were also seen in all areas. The blood vessels were dilated, and the perivascular spaces were increased in size. The endothelial cells were swollen, but no budding was evident. The vessel walls showed minimal hyaline changes.

The occipital lobe was similarly involved with a laminar loss of cells in the calcarine fissure. The neurons were shrunken and small. Astrocytes and scattered microglia were also present in the cortex. The blood vessels were made conspicuous by endothelial swelling.

Sommer's sector of the hippocampus revealed a minimal loss of pyramidal cells, but those which were present appeared to have normal appearing nuclei and cytoplasm. The vessels in this region were congested and showed minimal swelling of the endothelial cells. The cerebellum (Fig. 2) revealed a loss in the number of Purkinje cells with eosinophilic changes in the cytoplasm. Many Purkinje cells were swollen and fragmented. Necrosis was evident in Bergmann's layer, as well as an increase in astrocytes. All of the folia exhibited a loss of cells in the granular layer with some areas affected more than others. Astrocytes and microglia were increased in number throughout the molecular layer. The medial portion of the dentate nucleus was involved by a marked loss of cells and in those that remained there was pallor of the nuclei with homogeneous powdering of the Nissl substance.

The basal ganglia, particularly the globus pallidus, showed a minimal loss of cells with the neurons showing shrinkage of the cytoplasm in some areas.

CASE 2. A. D., a 50 year old white housewife, was admitted to another hospital on June 8, 1955 for treatment of a paranoid state with electroshock. She was given 3.0 cubic centimeters of curare intravenously prior to electroshock. Five minutes later, she became cyanotic; neither pulse nor heart sounds were present. Artificial respiration was started and 2.0 cubic centimeters of adrenalin were administered into the heart muscle. Eight minutes later, the pulse was perceptible. Her blood pressure, pulse, and respirations soon became stabilized. Within a few hours the patient began to vomit bright red and dark blood. She was given blood, fluids, and plasma intravenously but lapsed into coma and died 3 days after her episode of cardiac arrest.

At postmortem examination, in the stomach a small gastric ulcer with multiple small erosions of the gastric mucosa was present. A well healed, inactive, indurated ulcer was found in the duodenum. The brain and portion of dura, after fixation in 10 per cent formalin, weighed 1,280 grams. The vessels over the hemisphere were congested. The cerebellar tonsils were prominent but not notched. The unci were prominent bilaterally to a depth of 5 millimeters. On coronal sections, no gross abnormalities were noted.

Upon microscopic examination, in the frontal cortex, there was a diffuse loss of neurons throughout.

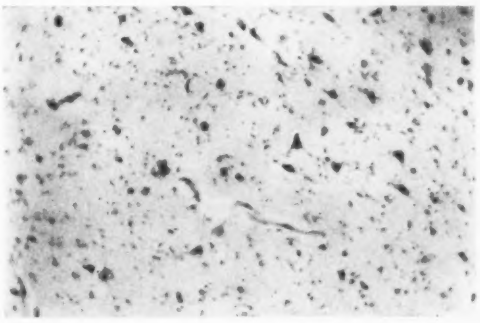

FIG. 1. Case 1. Section through frontal cortex demonstrating loss of neurons in the fifth layer. Astrocytes are increased and there are dilated capillaries.

Many neurons were shrunken, their nuclei and cytoplasm exhibiting hyperchromatic staining qualities. Few normal neurons were evident and "ghost cells" were prominent throughout the cortex. The cell loss appeared to be most severe in layers III and V. The capillaries were prominent with endothelial swelling, but no proliferation was noted.

The occipital cortex revealed an almost complete loss of cells throughout all laminae with the calcarine area most severely involved. In some areas, no recognizable neurons were present. The blood vessels were quite prominent in all portions of the cortex with endothelial swelling and congestion. Microglia and astrocytes were found to be present in increased numbers.

In the hippocampus (Fig. 3), areas of rarefaction were present with a diffuse loss of cells. The remaining cells were shrunken, the nuclei were hyperchromatic, and eosinophilic staining qualities were found in the hematoxylin and eosin preparations. Elongated microglial cells and astrocytes with pale, swollen nuclei were in abundance in the cortex. Proliferation of satellite cells to the point of neuronophagia was observed in almost every section of the hippocampus. The blood vessels in this region showed some thickening of the media and swelling of the endothelium (Fig. 4).

The cerebellum was involved with necrosis of many of the folia. The Purkinje cells were fragmented, reduced in number, and showed eosinophilic staining qualities of the cytoplasm and nucleus. There was rarefaction in Bergmann's layer with some increase in microglial cells. The molecular layer had an increase in the number of microglial cells. The dentate nucleus was diffusely involved with loss in number of cells and pallor of the remaining nuclei. The capillaries were prominent with congestion and swelling of the endothelium.

In sections of the basal ganglia, neurons were reduced in number with shrinkage of the cytoplasm.

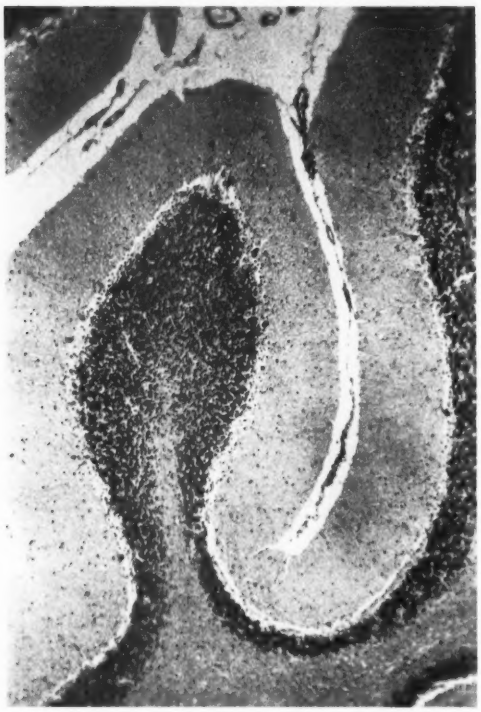

FIG. 2. Case 1. Cerebellar cortex. There is a decrease in the number of Purkinje cells with fragmentation and swelling of those that remain. There is also rarefaction of Bergmann's layer, as well as an increase of astrocytes and microglia in the molecular layer.

The cell loss was not nearly as severe as in the frontal lobes, occipital cortex, or cerebellum.

In the pons, a spotty loss of nuclei was found with eosinophilic changes in the nuclei and cytoplasm.

PATHOLOGY

These cases represent cardiac arrest from diverse causes, as well as variability in the duration of cardiac arrest and period of survival. In the first case, the cardiac arrest was of 4 minutes' duration with a survival period of 27 hours; while the cardiac arrest in the second instance was of 8 minutes' duration with a survival period of 3 days. The cerebral changes in both cases exhibited a striking similarity but with the changes more pronounced in the second case.

The vulnerability of the cerebral cortex to the acute anoxia is demonstrated by the changes in the occipital and frontal cortex. In these areas, a laminar loss of cells was found involving particularly laminae III and V with the occipital cortex showing a greater degree of involvement in both cases. The calcarine area in the second case contained no normal appearing neurons and exhibited dilated and proliferated blood vessels with an increased number of astrocytes and microglial cells in the cortex. Investigation of the various effects of anoxia upon the brain has shown that the "unit lesion" of cerebral anoxia is a focal loss of cells involving the intermediate cortical laminae. In cases reported by Howkins, McLaughlin, and Daniel and Löken, Haymaker, and Paulson, a similar laminar loss of cells was noted. In Courville's case of cardiac arrest for 10 minutes and survival time of 23 days, there were areas of subtotal necrosis in the cortex and globus pallidus.

Actually, this stage was the end result of the coalescence of the laminar loss of cells which occurred during the reparative period of the brain in the longer survival time. Experimentally Gildea and Cobb occluded the vertebral and subclavian arteries in cats for varying intervals of time and observed a focal loss of cells in lamina V. Gomez and Pike observed a loss of small pyramidal cells in similar experiments with cats. Weinberger, Gibbon, and Gibbon found no adverse effects to the brains of dogs, if the circulatory arrest persisted no longer than 3 minutes and 10 seconds, but if this period of circulatory arrest persisted for longer intervals, blindness was encountered clinically and microscopic examination of the cortex revealed marked involvement of laminae III and IV. Grenell found that by occluding the cerebral circulation in dogs with a cervical cuff, laminae III and IV were severely involved, but the brain-stem and hypothalamus were more resistant. Desmaret and L'hermitte noted lipochrome changes in the neurons of the frontal and occipital lobes and cerebellar cortex in their case.

The cerebellum was involved in both of the cases in this report showing a loss of

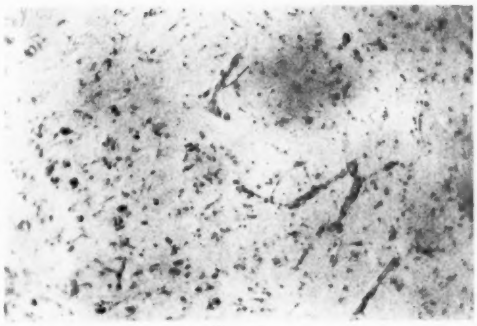

FIG. 3

FIG. 4

FIG. 3. Case 2. Ammon's horn. There is a loss of pyramidal cells with an abundance of astrocytes. The blood vessels are increased in number.
FIG. 4. Case 2. Hippocampus. A vessel with proliferated endothelial cells.

Purkinje cells, as well as varying degrees of degeneration. Eosinophilic changes of the nucleus and cytoplasm were indicative of the early anoxic changes described by Spielmeyer. There was rarefaction necrosis of Bergmann's layer as well as an increase in glial elements. The molecular layer was prominent with microglia and astrocytes in the second case. The dentate nucleus was involved in both cases with loss of neurons and pallor of those that remained.

The hippocampus was severely involved in Case 2 with a marked loss of pyramidal cells in Sommer's sector. Satellite cells were present in every area and the few nuclei revealed fragmentation, pallor, and eosinophilic staining qualities with the hematoxylin and eosin stain. The vessels in this region were prominent with endothelial swelling and proliferation.

The basal ganglia in both cases and the pons in the second case revealed a diffuse loss of neurons throughout with dilated congested vessels.

No areas of actual softening were noted in either case as the patients did not survive long enough to develop these changes.

DISCUSSION

In 1874 Schiff, a German physiologist, administered chloroform to dogs in excessive amounts until he produced an acute cardiac arrest and then after varying intervals of time, massaged the exposed heart to restore cardiac pulsation and respiratory movements. The first attempt to resuscitate a human heart occurred in 1899 by Niehaus, but was unsuccessful. Since that time, numerous cases of cardiac arrest with resuscitation have been reported. Barber and Madden (1), in reviewing the literature up to 1945, collected 143 cases in which complete recovery was obtained in 48.

In cardiac arrest, a unique situation occurs in the brain. There is a sudden and acute cessation of blood to the brain, no further nutrients are supplied, and cerebral metabolites accumulate in large quantities. The anoxia which results has a varied effect upon different parts of the central nervous system. The cortex of the brain and cerebellum in these cases appeared to be most sensitive to the oxygen deficiency which is in keeping with observations of Schöltz, who described similar areas of "selective neuronal necrosis" in the frontal cortex, cerebellum, and Sommer's sector of Ammon's horn. As the period of anoxia is prolonged, the changes are more diffuse in the brain and there is less selectivity present.

By an analysis of these cases, the degree of involvement becomes more apparent. In Case 1, a generalized hypoxemic anoxia was produced by a gradual drop in blood pressure and an incomplete airway during the surgical procedure. Cardiac arrest of 4 min-

utes' duration then occurred producing further anoxia.

In the second case, there was, in addition to the generalized anoxia of the electroshock treatment and curare, an episode of cardiac arrest of 8 minutes' duration, which was followed by gastrointestinal hemorrhage producing more anoxia. The changes of a greater degree in this case were probably due to anoxic and anemic anoxia superimposed upon cardiac arrest of longer duration.

SUMMARY

Two cases of acute cardiac arrest are reported in humans in which there was evidence of irreversible changes of the brain by microscopic examination. These observations are of importance to the surgeon who is confronted with the situation of cardiac arrest during an operative procedure, for speed is essential in restoring circulation by cardiac massage. The crucial period for complete recovery is 3 minutes from time of cardiac standstill to the moment of cardiac massage. With longer periods, selective involvement of the frontal lobe, occipital lobe, cerebellum, and hippocampus may occur as described in our cases of cardiac arrest of over 4 minutes' duration.

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A VASCULAR MECHANISM FOR MAINTAINING TESTICULAR TEMPERATURE BY COUNTER-CURRENT EXCHANGE

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CORRELATION of structure and function remains one of the basic approaches to an understanding of biologic processes. Physical mechanisms which affect function are interesting in their own right. Counter-current exchange is such a mechanism.

The phrase "counter-current exchange" as used by Scholander (17) expresses the principle of transfer of heat between fluids of different temperatures flowing in opposite directions in adjacent conduits, as shown in Figure 1a. That heat from the warm fluid in the lower tube in this diagram will be lost to the cooler fluid in the adjacent tube is readily apparent.

The efficiency of such a system at given temperatures depends, among other factors, on the intimacy of the conduits, and on the length of time that the contained fluids are in association, hence on the rates of flow and on the length of the associated conduits. Increasing the surface across which heat can be conducted, as by increasing the number of tubes in proximity to each other (Fig. 1b), will increase the exchange of heat. Counter-current exchange is well known to engineers, who use it for such purposes as to preheat with hot exhaust gases the water coming into a steam boiler, thus utilizing heat energy which would otherwise be wasted. The mechanism may operate not only for the exchange of heat, but also for the transfer of dissolved substances across semipermeable membranes.

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Abridgment of portion of thesis submitted by Dr. Dahl to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pathology.

Dr. Dahl is on assignment from the United States Air Force.

Although Claude Bernard suggested 80 years ago that body heat was conserved by its transfer from arteries to the centripetally flowing veins, counter-current exchange as an important mechanism in the heat economy of animals has received serious consideration from biologists only during the past 2 decades. Multichannel arterial and venous networks in the long legs of wading birds, in the flippers and tails of whales and other aquatic mammals, and in the extremities of temperature-sensitive mammals with low metabolic rates, such as the sloth, were described anatomically in the nineteenth century and earlier according to Scholander (17) and Fawcett. These networks of intermingled arteries and veins were called "Wundernetze" by nineteenth century German comparative anatomists. Wundernetze becomes "retia mirabilia" in Latin, and "wonderful networks" in English.

The remarkable efficiency of these vascular networks in preventing loss of heat from the exposed body surfaces of animals has been well described by Scholander (17–19). He (16) has explained, also, how similar vascular structures in certain deep-sea fishes are effective in maintaining oxygen within their swim bladders against great differences in oxygen pressure across the swim bladder wall.

Even in the absence of such complex vascular structures in the extremities of man and other higher mammals, it seems that there is significant transfer of heat from arterial blood to the cooler blood returning from the periphery in the venae comitantes. In 1927 Bazett and McGlone (3) found that the blood in both the femoral artery and

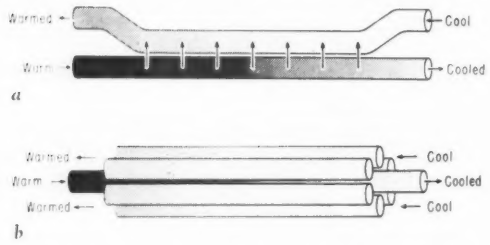

FIG. 1. Counter-current exchange. a, Transfer of heat from warm fluid to a cooler fluid flowing in the opposite direction in an adjacent conduit. b, Increasing the number of adjacent conduits increases exchange of heat by increasing the surface across which heat can be conducted.

vein in the dog was considerably cooler than the rectal temperature, and that the venous blood was somewhat cooler than the arterial. They stated that the transfer of heat from arteries to veins might account for low temperatures found by them in muscles of human beings. Bazett (1), in 1938, suggested that one of the mechanisms for lowering skin temperature in cold weather is the shunting of venous blood from superficial veins to the venae comitantes, resulting in cooling of the blood within the arteries which these veins accompany. Forster, Ferris, and Day, in studies using a combination plethysmograph and calorimeter, measured blood flow in the human hand and heat lost from the hand by radiation, convection, and evaporation. They calculated that there must be considerable cooling of arterial blood before it enters the hand.

Bazett and others (2) measured intravascular temperatures in the extremities of man directly by means of thermocouples in fine flexible tubing and described gradients of 0.3 degree C. per centimeter and more in the arteries of the arm. They found that if the blood in veins accompanying these arteries was cold, compression of the arm to hinder venous flow caused a rise in intra-arterial temperature proximal to the point of compression.

During studies of the testis and spermatic cord of the human infant and of the rat, we were struck by the arrangement of the numerous veins of the pampiniform plexus about the internal spermatic artery. This venous plexus seemed admirably situated for the removal of heat from the blood in the internal spermatic artery.

Physicians are all aware of the pampiniform venous plexus as an anatomic entity. Surgeons often excise parts of this plexus if it develops varices and becomes bulky, pendulous, and painful. Everyone is also aware, since Moore's (14) classic studies in the 1920's, that the testes of mammals with high body temperatures must be situated outside the abdominal cavity for spermatogenesis. Undescended testes in the human being produce no sperm. Moore (13) and Wangensteen demonstrated that when the testes of a guinea pig or an adult dog are surgically placed within the animal's abdominal cavity, the testicular tubular epithelium degenerates rapidly. According to Wislocki, mammals with intra-abdominal testes have, in general, body temperatures below those of mammals with scrotal testes. The elephant, whose testes are situated within the abdomen, has a body temperature of approximately 36 degrees C., considerably higher than that of most mammals with undescended testes. This temperature is nearer to the 34.5 degree C. temperature of the dog's testes, recorded subsequently in this paper, than to the dog's 38 degree C. central temperature.

STUDIES AND RESULTS

With these concepts in mind, and with a certain skepticism concerning the efficiency of the scrotum as a heat dissipating structure, we undertook measurements of the temperature of the blood in the internal spermatic artery of the dog to determine the temperature gradient within this vessel. We were unaware, until after we had completed our experiments, that this problem had been approached previously. While assembling our data for presentation, we found that Harrison and Weiner (9) had suggested in 1948 that the anatomic relationship of the testicular artery and veins appeared to provide a likely mechanism for insuring an abdominotesticular temperature gradient. In

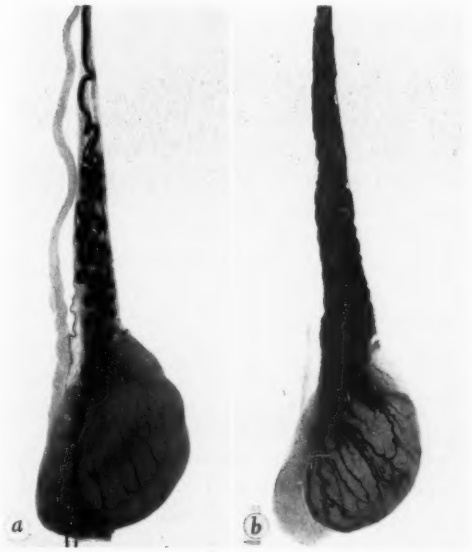

FIG. 2.

FIG. 2. Testis and spermatic cord of the dog, cleared by the Spalteholz method. a, The extreme tortuosity of the internal spermatic artery is brought out by an injection of latex. b, The artery, after injection of red latex into it, appears pale, winds in and out among the numerous veins of the pampiniform plexus, into which blue latex has been injected.

FIG. 3.

FIG. 3. Cross section of the internal spermatic artery of the dog 1 centimeter above the head of the epididymis. a, The single internal spermatic artery has been sectioned through an S loop, so that it appears as 3 separate arteries surrounded by veins of the pampiniform plexus (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain, hereafter abbreviated to ELVG; ×15). b, Enlargement to show the intimate association of the artery and numerous veins (ELVG; ×40).

the following year, these authors (10) used thermocouples to measure the temperature within the internal spermatic artery and an accompanying vein at a single level as near the abdominal wall as possible in 3 goats, 2 rams, and 2 dogs. Their results will be discussed subsequently.

In the dog, the internal spermatic artery is highly tortuous over a variable length immediately proximal to the testis. It winds in and out among the extremely numerous veins of the pampiniform plexus (Fig. 2). The intimate association of the artery and veins and the great number of the latter are best appreciated from cross sections (Fig. 3).

Temperatures of the operating room air, scrotal skin, testicular parenchyma, blood in the distal part of the internal spermatic artery, and of the blood in the aorta at the level of origin of the internal spermatic arteries were determined simultaneously in large mongrel dogs (weighing 18 to 29 kgm.) anesthetized with pentobarbital sodium. The room temperature was obtained with a mercury thermometer. All other temperatures were obtained with thermistor thermometers sensitive to 0.05 degree C. These were calibrated carefully against a standard mercury thermometer (standardized by the National Bureau of Standards) before and after each experiment. All observed temperatures are reliable to within 0.1 degree C.

Temperatures of the skin of the scrotum were obtained by inserting a thermistor protected by a polyvinyl sheath immediately beneath the epidermis on the anterior of the dog's scrotum. The temperature of the testicular parenchyma was recorded from a thermistor in a 17 gauge needle inserted through the scrotal skin and tunica albuginea into the inferior pole of the testis to a depth of 1 centimeter. A 2 centimeter incision was made in the scrotum laterally to expose the free border of the epididymis in its central portion. The internal spermatic artery coursing in the tunica vasculosa of the testis usually emerges from beneath the epididymis at this point. This artery was pierced with a 25 gauge needle containing a thermistor in its tip. The point of the needle, which contained the thermistor, was inserted as far proximally into the internal spermatic artery as the configuration of that vessel permitted to avoid recording reduction in blood temperature attributable to loss of heat to the testicular substance. Temperature of the aortic blood was recorded from a thermistor in a polyvinyl sheath inserted through the femoral artery to the estimated level of origin of the internal spermatic arteries.

Temperatures of the scrotal skin, testicular parenchyma, and within the internal spermatic artery and aorta were recorded as nearly simultaneously as the

TABLE I.—TESTICULAR TEMPERATURE GRADIENT IN THE DOG

		Temperature in degrees, centigrade				
Dog	*Testis*	*Room air*	*Scrotal skin*	*Testicular parenchyma*	*Internal spermatic artery*	*Aorta*
1	Rt.	24.2	33.0	34.7	35.2	—
	Lt.	24.3	33.5	35.1	35.5	—
2	Rt.	24.2	34.5	35.2	35.4	38.2
	Lt.	24.4	33.7	33.8	34.9	38.2
3	Rt.	24.5	31.6	34.3	35.3	39.2
4	Rt.	24.2	32.4	33.7	34.6	37.2
	Lt.	23.8	32.8	33.8	34.2	36.6
5	Rt.	24.0	33.4	35.3	35.6	38.3
	Lt.	23.7	32.0	33.9	34.8	38.2
6	Lt.	23.6	32.3	35.0	35.2	38.3
7	Lt.	23.3	31.0	34.8	35.1	38.6
8	Rt.	24.4	33.6	34.9	35.0	37.6
	Lt.	24.8	32.9	34.1	34.4	37.3
Average		24.1	32.8	34.5	35.0	38.0

TABLE II.—TEMPERATURE IN INTERNAL SPERMATIC ARTERY AND ADJACENT SOFT TISSUE IN THE DOG

		Temperature in degrees, centigrade					
		Soft tissue, distance from testis				Internal spermatic artery, distance from testis	
Dog	*Testis*	*9 cm.*	*5 cm.*	*1 cm.*	*Aorta*	*9 cm.*	*1 cm.*
6	Rt.	37.7	37.7	36.7	38.0	36.7	35.4
	Lt.	37.8	37.6	37.5	38.0		35.2
7	Rt.	37.8	37.7	37.4	39.1	36.7	
	Lt.	37.8	37.7	37.5	39.0		35.2
9	Rt.	38.2	37.9	37.3	38.4	37.5	
	Lt.	38.3	37.8	37.1	38.4	37.8	
Average		37.9	37.7	37.3	38.5	37.2	35.3

TABLE III.—EFFECT OF INTERRUPTION OF BLOOD FLOW IN THE PAMPINIFORM PLEXUS ON TEMPERATURE IN THE INTERNAL SPERMATIC ARTERY

			Temperature in degrees, centigrade				
Dog	*Testis*	*Pampiniform plexus*	*Room air*	*Scrotal skin*	*Testicular parenchyma*	*Internal spermatic artery*	*Aorta*
10	Rt.	Severed	24.4	32.8	34.0	38.7	40.1
		Intact	24.4	31.5	33.3	35.6	40.0
		Difference		1.3	0.7	3.1	
11	Rt.	Severed	23.9	34.0	35.6	36.9	38.4
		Intact	24.0	33.0	35.4	35.6	38.3
		Difference		1.0	0.2	1.3	
12	Rt.	Severed	24.9	33.0	35.1	38.6	40.1
		Intact	24.8	31.6	34.3	36.1	40.0
		Difference		1.4	0.8	2.5	
Average temperature increase				1.2	0.6	2.3	

TABLE IV.—DECREASE IN TEMPERATURE GRADIENT WITHIN THE INTERNAL SPERMATIC ARTERY FOLLOWING INTERRUPTION OF THE PAMPINIFORM VENOUS PLEXUS (TEMPERATURE IN DEGREES, CENTIGRADE)

	Pampiniform plexus intact			*Pampiniform plexus interrupted*		
Dog	*Aorta*	*Internal spermatic artery*	*Difference*	*Aorta*	*Internal spermatic artery*	*Difference*
10	40.0	35.6	4.4	40.1	38.7	1.4
11	38.3	35.6	2.7	38.4	36.9	1.5
12	40.0	36.1	3.9	40.1	38.6	1.5
Average	39.4	35.8	3.7	39.5	38.1	1.5

act of reading needle deflections on the separate galvanometers permitted.

Temperatures observed at the various sites in 13 testes from 8 dogs are presented in Table I. Each of the temperatures presented in this tabulation is an average of at least 3 observations. The temperature of the blood in the internal spermatic artery was 3 degrees C. (5.4 degrees F.) lower than the temperature in the aorta and was within 0.5 degree C. of the average temperature of the testicular parenchyma. This is immediately apparent in Figure 4.

The demonstration of a temperature gradient within the internal spermatic artery conclusively establishes only that there is a loss of heat from the blood within that vessel. Additional data to ascertain that the heat from the blood in the internal spermatic artery is indeed lost to the veins, and not simply to the tissues of the body wall, were acquired.

In 3 large mongrel dogs, temperatures of the soft tissue immediately adjacent to both the right and left spermatic cords were measured by means of a thermistor thermometer in a 25 gauge needle inserted through the skin low on the abdomen to positions immediately medial, lateral, and then superficial to the palpated spermatic cord at sites 9, 5, and 1 centimeter above the superior pole of the testis. The temperature of blood in the aorta was determined as previously. A 2 centimeter length of spermatic cord was surgically exposed, and a short length of internal spermatic artery was carefully dissected from the surrounding veins, to permit insertion of a 25 gauge needle thermistor under direct vision.

Temperatures within the internal spermatic artery 9 and 1 centimeter proximal to the testis are given in Table II. As in Table I, each of the recorded temperatures represents the average of 3 or more observations. Temperatures given for the soft tissue are averages from immediately medial, lateral, and superficial to the spermatic cord. The average temperature in the spermatic artery, 9 centimeters proximal to the testis, was 37.2 degrees C., 0.7 degree cooler than the surrounding tissue; 1 centimeter proximal to the testis, the blood in the internal spermatic artery was 2.0 degrees cooler than

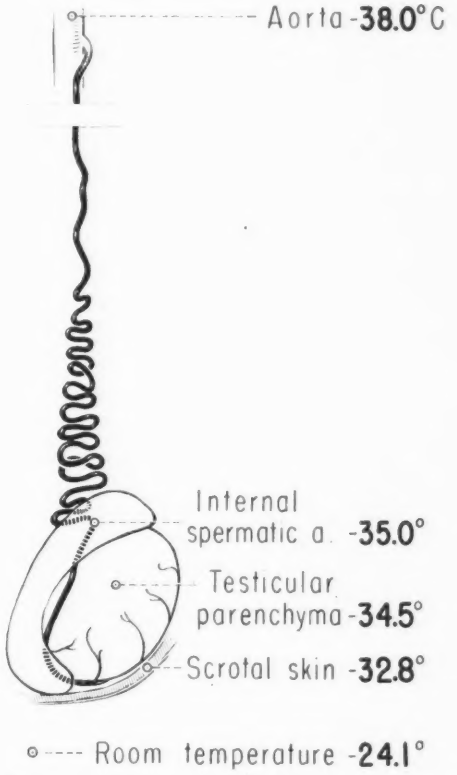

FIG. 4. Average temperature gradient from aorta to external environment determined from measurements in 13 testes from dogs at the sites indicated.

the surrounding tissue. It is obvious that heat from the internal spermatic artery is not transferred to tissue of a greater temperature.

Additional experiments were performed to establish this point. If heat is indeed transferred from arterial to venous blood in the spermatic vessels, then the gradient within the internal spermatic artery should be significantly affected by preventing cooled venous blood from utilizing countercurrent channels.

Heparin, 10 milligrams per kilogram of body weight, was administered intravenously to 3 dogs. A short segment of spermatic cord, from 3 to 5 centimeters above the superior pole of the testis, was exposed surgically. The internal spermatic artery was carefully dissected from the surrounding veins with-

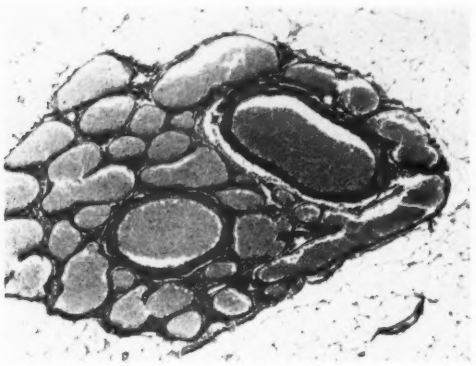

FIG. 5. Internal spermatic artery and accompanying veins of a rat. The single artery has been cut through an S loop, so that it appears as two separate arteries, each completely surrounded by veins (ELVG; ×44).

out rupture of the latter, an extremely tedious procedure. The vessels were carefully replaced and the margins of the incision were approximated. Temperatures of the scrotal skin, testicular parenchyma, distal internal spermatic artery, and aorta were determined as in previous experiments, at the sites shown in Figure 4. All thermistors were left in place. The pampiniform plexus was clamped, and its veins were divided distal to the clamp. The freely bleeding distal cut ends of the veins were brought outside the incision, and the margins of the wound were approximated. Temperatures were recorded when they had become stable.

Data from these experiments are presented in Table III. Each of the recorded figures is an average of 3 or more observations. After the venous blood had been diverted from counter-current channels, the temperature of the blood within the distal spermatic artery was increased by an average 2.3 degrees C. The wide variation of the rise in temperature within the internal spermatic artery of these 3 dogs (3.1, 1.3, and 2.5 degrees) may be explained by referring to Table IV. In each dog the intra-arterial temperature following interruption of the pampiniform plexus was increased to a level which differed by 1.4 to 1.5 degrees from that within the aorta. Following division of the veins, the average temperature within the internal spermatic artery (38.1 degrees C.) was higher than that of the soft tissue adjacent to the spermatic cord recorded in Table II. Concomitant with the rise in intra-arterial temperature, the scrotal skin and testicular parenchyma became warmer by 1.2 and 0.6 degree C. respectively.

COMMENT

Measurements of the temperature of the blood within the veins of the pampiniform plexus were not obtained for two reasons: (1) A rising temperature gradient along these veins, from the testis proximally, would neither confirm nor deny the transfer of heat from arterial to venous blood. Such a gradient within the veins could be explained by transfer of heat from surrounding tissue; (2) There would be no assurance that any vein selected for temperature determination had been in close proximity to the internal spermatic artery for a significant distance. Laborious dissections would be required to establish the relationship of any selected vein to the internal spermatic artery.

The relatively small increase in temperature of the testicular parenchyma following division of the pampiniform plexus in these experiments (Table III) requires comment. With an average gain of 2.3 degrees C. in intra-arterial temperature following this procedure, the testicular temperature rose only 0.6 degree C. The most likely explanation of this apparent discrepancy seems to be that blood flow to the testis is reduced by the experimental manipulations. Short periods of venous occlusion during dissection of the pampiniform plexus are unavoidable. Miflet found that testicular engorgement and edema rapidly follow occlusion of the pampiniform plexus. Although the stony firmness which results from prolonged venous occlusion was not observed in the testes of any dog included in this study, these organs were more turgid at the conclusion of the experiments than at their beginning. Testicular edema would be expected to reduce arterial flow by compression of small vessels.

Spasm of the internal spermatic artery following its surgical manipulation was at times severe and prolonged. Kinmonth used

local applications of papaverine hydrochloride to relieve such spasm and increase arterial blood flow through the treated vessel. Because this substance had not been used in the preceding experiments, it was not applied in the 3 dogs under discussion. In all of our experiments, temperatures were recorded only after they had become stable. Nevertheless, with all incisions closed, it was impossible to exclude residual or recurrent arterial spasm. Kinking or torsion of the internal spermatic artery during its replacement in the wound following dissection of the pampiniform plexus would produce a reduction in arterial flow to the testis. These factors, testicular engorgement and edema, arterial spasm, kinking, or torsion, may all act to reduce arterial blood flow and to decrease the amount of heat brought to the testis. With no apparent experimental artifacts acting to increase heat brought to the testis, the rise in temperature of this organ following section of the pampiniform plexus might be expected to be small.

The average increase of 1.2 degrees C. in temperature of the scrotal skin following pampiniform plexus interruption permits an attractive hypothesis to support the supposition that reduced blood flow to the testis explains the small rise in testicular temperature. Blood shunted via anastomoses from the internal spermatic artery to the pudendal branches supplying the scrotum could raise the temperature of that organ without altering testicular temperature greatly. There is disagreement, however, concerning the existence of such anastomoses in the dog according to Neuhof and Mencher.

From their measurement of temperatures within the internal spermatic artery and an accompanying vein at a single level near the abdominal wall in 7 animals, Harrison and Weiner (10) found that the temperature of the arterial blood was slightly less than the abdominal temperature, and that venous blood was cooler still. When they heated the testis directly, intravascular temperatures, both arterial and venous, rose. When they cooled the testis, intravascular temperatures decreased. These authors did not demonstrate that, at physiologic testicular temperatures, there was a gradient within the internal spermatic artery which could not be related to the temperature gradient within the adjacent tissues. They stated that their evidence of "precooling" of arterial blood was indirect, and that proof of exchange of heat between arteries and veins within the spermatic cord would necessitate calorimetric studies of heat flux within the testis and its comparison with the flow of heat carried by the blood stream.

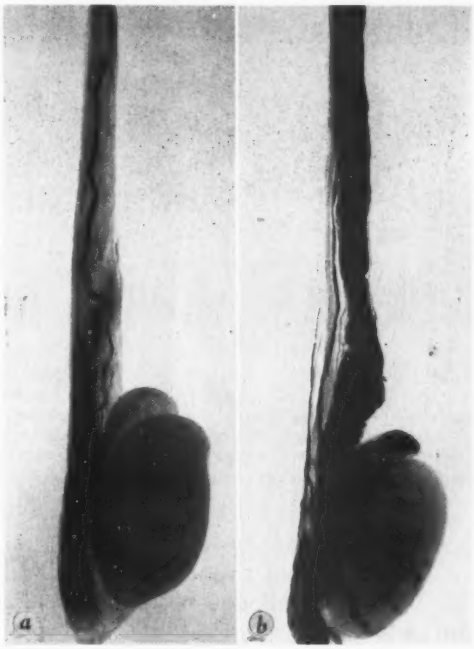

FIG. 6. Testis and lower spermatic cord from human being cleared following injection of latex. a, The internal spermatic artery appears relatively straight. b, The numerous veins of the pampiniform plexus surround the artery and hide most of it from view.

Methods for such determinations are not at present available. Further, we do not believe that quantitative studies of heat exchange, with their inherent errors, would offer more conclusive proof of the loss of heat from arteries to veins than does the demonstration of an intra-arterial temperature

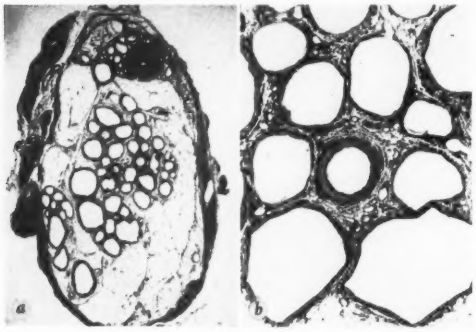

FIG. 7. Cross section of spermatic cord from human being 1 centimeter above the head of the epididymis. a, The internal spermatic artery has divided into 3 branches, which are surrounded by veins of the pampiniform plexus (ELVG; ×2). b, One of the arterial branches at a slightly different level, showing that vessel completely surrounded by thin-walled veins (ELVG; ×15).

gradient which is steeper than that of the adjacent soft tissue, and which is greatly reduced when counterflow of venous blood is interrupted.

The anatomic arrangement of the blood vessels of the testis in many mammals, including man, suggests that the principle of counter-current exchange is valid also in these animals and that, in conjunction with the position of the testes and the structure of their coverings as indicated by Crew, it aids in maintaining a testicular temperature suitable for spermatogenesis. Harrison (8) has provided beautifully accomplished angiograms of the arterial supply to the testis in many mammalian species.

In the rat as in the dog, the scrotum holds the testes snugly against the lower part of the abdominal wall with, consequently, relatively little scrotal skin for the dissipation of heat to the environmental air. In the rat as in the dog, the internal spermatic artery is highly tortuous and is completely surrounded by veins (Fig. 5). The scrotum in man is completely pendant and presents a relatively much greater surface to the environment. Man's internal spermatic artery is only minimally convoluted. Nevertheless, this artery in man is also surrounded entirely by veins with counterflowing blood (Figs. 6 and 7), and these are effective through a much longer length of spermatic cord than in either the dog or the rat. Only direct measurements of intra-arterial temperature can determine the nature of the temperature gradient within the internal spermatic artery in man.

SUMMARY

The veins of the pampiniform plexus, arranged about the internal spermatic artery, form an anatomic counter-exchange unit in many mammals, including the rat, the dog, and man. This arrangement might be expected to result in a reduction in the temperature of the blood within the internal spermatic artery.

That, in the dog, such cooling does in fact occur is shown by the demonstration of a temperature gradient within the internal spermatic artery. Temperature of the blood decreases an average 3 degrees C. during its flow through the length of this artery. The intra-arterial temperature gradient is steeper than the gradient within surrounding tissue; hence heat is not dissipated from the blood to the body wall. The intra-arterial temperature gradient is largely abolished when the pampiniform plexus is interrupted, preventing cooled venous blood from utilizing counter-current channels.

The mechanism of counter-current exchange, by cooling arterial blood prior to its arrival in the testis, relieves the scrotum of part of its burden of dissipating heat.

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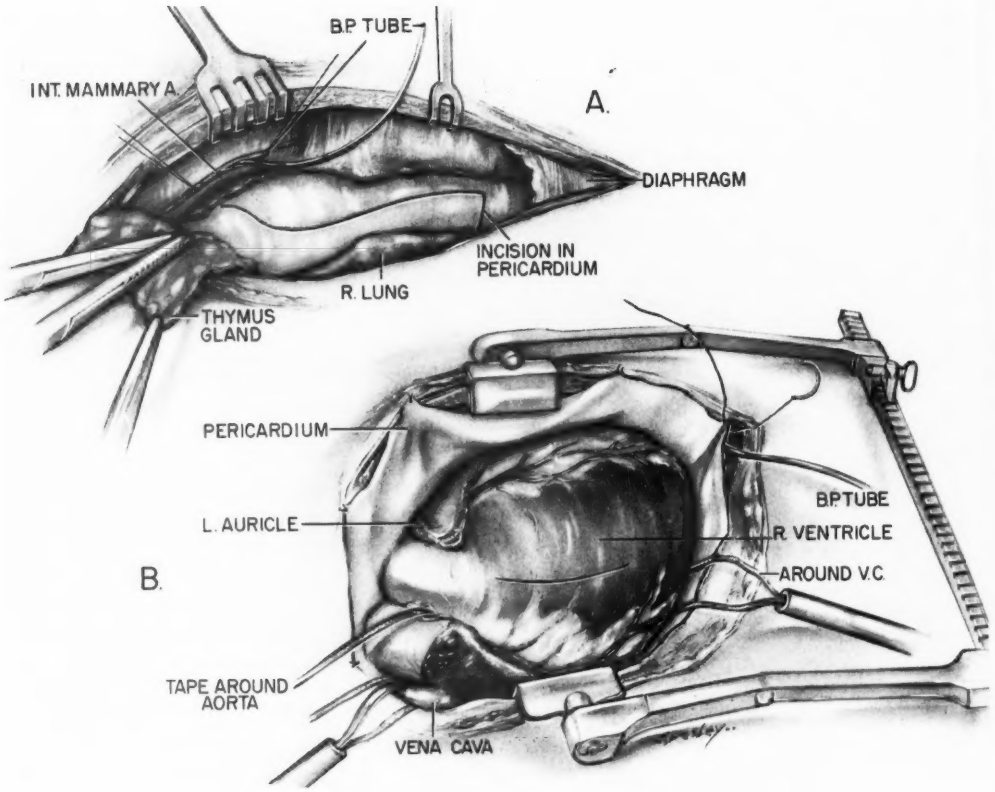

FIG. 3. Internal mammary artery cannulation. A, Either the left or right internal mammary artery is exposed and routinely cannulated with an appropriately sized polyethylene tube and connected to a suitable pressure recording apparatus to give a continuous record of central aortic pressure conveniently. The thymus, if large, is split in its avascular midline to allow the lobes to fall out of the way. The pericardial incision is shown with the lateral extension inferiorly to allow exposure of the inferior vena cava. B, The hinged retractor has been inserted. The pericardial edges have been sewed to the sternal edges elevating and marsupializing the heart resulting in the excellent exposure to the right ventricle, pulmonary artery, and aorta shown. The cavae and aorta have been looped with cotton tapes.

Use of Median Sternotomy with Femoral Artery Cannulation in Open Cardiac Surgery.—C. Walton Lillehei and Richard H. Cardozo.

USE OF MEDIAN STERNOTOMY WITH FEMORAL ARTERY CANNULATION IN OPEN CARDIAC SURGERY

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THE BILATERAL anterior thoracotomy incision between or through the bed of the fourth or fifth ribs with transverse sternotomy and cannulation of the left or right subclavian artery was utilized in the majority of the first 400 patients undergoing intracardiac surgery with the pump-oxygenator at the University of Minnesota Hospitals.

Since 1957, we have employed the vertical median sternotomy routinely in approaching the heart for the correction of ventricular septal defects, tetralogy of Fallot, pulmonic stenosis, aortic valve disease, coronary arteriovenous fistulas, and ruptured aneurysms of the sinus of Valsalva. Where wide exposure of the right atrium is required, such as for repair of atrioventricularis communis lesions, we have continued to employ either the bilateral thoracotomy with transverse sternal dividing incision or the right posterolateral approach. In those patients with atrial septal defects without appreciable pulmonary hypertension we prefer the bilateral incision, but in those in whom there is significant elevation of pulmonary resistance either the midline sternotomy or right posterolateral approach which enters only one pleural cavity is recommended.

For acquired heart disease involving the mitral valve, the right posterolateral approach through the bed of the fifth rib is preferred. The aortic valve may be well exposed either by this lateral approach or via the midline sternotomy. For combined lesions of the mitral and aortic valves the right lateral approach gives adequate exposure for open procedures upon both valves.

The femoral artery cannulation is, of course, necessary with the midline sternotomy but has been adopted also as the procedure of choice for all open heart procedures regardless of which incision is utilized because of its greater convenience and ease, the reduction of the amount of dissection within the chest, and the possibility that better perfusions to the brain occur by obviating the turbulence within the arch of the aorta that occurs when blood is introduced at that site.

In 300 patients in whom the femoral artery cannulation site was utilized, there has to date been not one significant complication such as bleeding, infection, aneurysm formation, or occlusion. The common femoral artery site for cannulation was first utilized in 1954 to 1955 in 45 adults who acted as donors for controlled cross circulation procedures (8). All of these survived, and in the period of 4 years or more that has now elapsed during which these patients have been observed there have been no late complications. This fact has further substantiated the feasibility and safety of this route provided careful technique is utilized.

In 1 older patient having open heart surgery for acquired valvular disease an arteriosclerotic obstruction was encountered in the iliac artery when the arterial catheter was inserted and therefore the subclavian was used instead. In several tiny infants the common femoral artery was so small that it was deemed advisable to use the subclavian instead.

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Although wide variations are encountered, the common femoral artery in the average patient tends to be slightly smaller in caliber than the subclavian. This fact has not proved to be any handicap in maintaining flow rates adequate to keep the systemic blood pressure normal, particularly with use of a positive displacement (occlusive) type pump. This benefit is one of the several reasons that pumps of positive displacement design are recommended as preferable for open heart work. The other advantages of this pump design have been commented upon elsewhere (1).

Median sternotomy is by no means a new incision having had scattered use for a variety of lesions within the mediastinum during the past 50 years or more. Holman has emphasized its value as an approach to the heart for pericardiectomy. Wangensteen has advocated midline sternotomy for treatment of certain patients with cancer of the breast, esophagus, or stomach. However, save for the report of Julian and associates upon its use in 4 patients, the significant superiority of median sternotomy over the bilateral transverse incision for many open heart procedures has not, as yet, received the general recognition it merits. Julian and associates advocated arterial cannulation by use of a homologous graft sewed directly to the thoracic aorta. This, we believe, is unnecessarily complex and hazardous for routine use and may, in part, account for the high mortality experienced in their initial report. Direct cannulation of the aorta might be useful for the rare situation in which the chest may have been entered through a median sternotomy and both femoral or iliac arteries are then found to be occluded (as could happen) in an older patient or unsatisfactory for use due to the unsuspected presence of coarctation of the aorta. Then, this method of direct cannulation would allow the surgeon to extricate himself satisfactorily from the difficulty. To date, such a circumstance has not occurred to us since we routinely and personally check the femoral pulsations in every patient preoperatively. In 3 patients this practice has resulted in the finding of an associated coarctation of the aorta, previously undiagnosed, in children referred for septal defect closure. In each instance, the coarctation was successfully managed along with the septal defect.

We have now used the median sternotomy approach in 200 patients and have been impressed with its advantages (5). Detailed reports upon the results in regard to the various lesions have been referred to elsewhere (3) and the over-all advantages may be summarized as follows: Excellent exposure of the heart, particularly the right ventricular outflow tract, pulmonary artery, and aorta, is obtained. The pleural cavities are not opened, and this avoidance of retraction, trauma, and drying of the lungs greatly reduces the incidence and severity of postoperative bronchial secretions and pneumonitis and has contributed to a significant reduction in morbidity and mortality from these sources, especially in poorer risk patients. Heat loss during operation is lessened. Shorter operating time is required to open and close the incision. Fewer sources for operative or postoperative bleeding are created. Smoother convalescence occurs as a result of freedom from incision or injury to any of the chest wall muscles. The more rigid repair of the sternum made possible by the midline division also results in greater ventilatory efficiency, much less postoperative pain, and substantially better coughing.

There have been surprisingly few disadvantages with this incision. Exposure to the right atrium is not as wide as with the transverse sternotomy, but is adequate for the necessary cannulations and for atrial (secundum) lesions. For patients with more complicated types of atrial defects such as atrioventricularis communis lesions the bilateral incision is utilized, but in those in whom severe pulmonary hypertension is also present the standard right posterolateral thoracotomy through the bed of the fourth or fifth rib is preferred. The midline sternotomy does not expose the left ventricle as well and therefore we have continued to use the bi-

lateral transverse thoracotomy for repair of left ventricular aneurysms.

Though at first it was thought that the approach to a patent ductus would be difficult through the midline incision, experience, obtained first from dissections in the autopsy room and subsequently in this series of patients, has indicated that the ductus area may be approached satisfactorily from the anterior intrapericardial route. This lesion has been found in approximately 10 per cent of patients with ventricular defects and is always searched for. If present, it is ligated or divided prior to the commencement of extracorporeal circulation. Likewise, an anomalous left superior cava is always looked for and, if present, is readily encircled and cannulated from the right atrium through the coronary sinus if large in size. In 2 children, one with the tetralogy of Fallot malformation and the other with an atrial secundum defect, the left cava was found to empty into the left atrium instead. In these instances, after a test period of clamping, the vessel was divided along with correction of the other defects.

For the female patient the midline incision may constitute a mild cosmetic problem. However, this fact is not worthy of any consideration in those patients in whom the midline incision may be expected to significantly reduce the operative risk, and with meticulous care to skin and subcutaneous closure this need be no more conspicuous than a carefully closed thyroidectomy incision. Moreover, the upper end of the incision may be made T shaped as suggested by Julian to minimize the scar. In the feminine patient with a heart lesion of the type for which a midline incision would be ordinarily preferred but who is an excellent risk from the standpoint of cardiac reserve, freedom from adhesions from previous surgery, no appreciable pulmonary hypertension, and absence of cyanosis, the conventional bilateral transverse incision is perfectly safe and is still used from time to time because of this cosmetic advantage.

Failure of the sternum to unite primarily has occurred only once in this entire series of 200 patients. This patient had a period of renal shutdown following a transfusion reaction with a consequent period of poor nutrition during the first 10 days of her recovery.

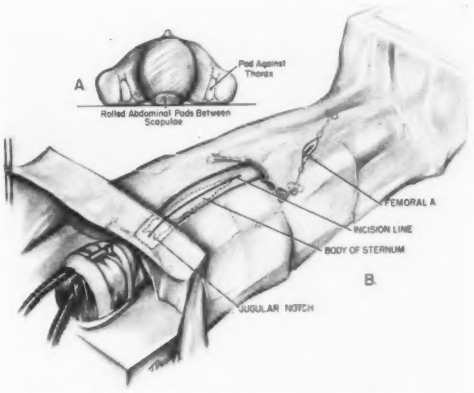

FIG. 1. Positioning and draping of patient for median sternotomy utilizing extracorporeal circulation.

The technical details of this approach have undergone considerable refinement since its inception, and others may find helpful the more detailed description to follow.

TECHNIQUE

After the patient has been accurately weighed and a polyethylene or teflon venous transfusion cannula has been inserted at the left saphenofemoral junction, he is placed in a supine position with a padded roll between the scapulae to allow them to fall back around the chest wall (Fig. 1A). The lower extremities are separated slightly and externally rotated. The various electrodes of the rectal thermistor and electrocoagulator are positioned, and the skin is prepared and draped to disclose the anterior thorax from the cricoid to the xiphoid and the right femoral triangle (Fig. 1).

Through an oblique incision just below the inguinal ligament the right femoral artery is isolated for a distance of several centimeters proximal to the profunda femoris and is encircled with an umbilical tape, and the wound covered. Attention is then directed to the chest where, as shown in Figure

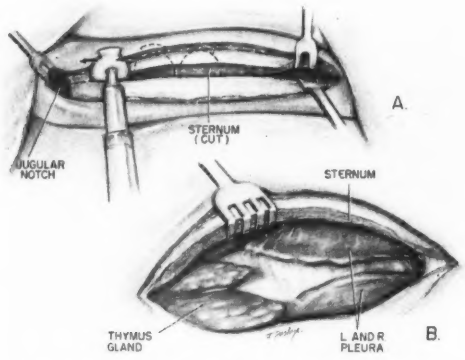

FIG. 2. A, The sternum is divided from below upward with a power saw and blunt retractors serve to elevate the sternum away from the heart which is often enlarged anteriorly. In order to obtain adequate separation of the sternal halves it is necessary to extend the incision down the linea alba well past the xiphoid. The use of a power saw rather than the Lebsche knife is less traumatic, and more accurate reapproximation of the sternum is possible. The incision in the sternum is carried through its entire length. (Sectioning the sternum transversely at the second or third interspace as sometimes recommended increases postoperative pain and the resulting repair is less firm.) B, After exposure is obtained, the pleural reflections are gently dissected from the pericardium without entering the pleural spaces.

1, a midline incision is made extending from 1.5 to 2 centimeters above the suprasternal notch to from 8 to 12 centimeters below the xyphoid depending upon the patient's size and costal configuration. The incision is carried through the subcutaneous and presternal fascial layers.

Hemostasis deep to the skin is then achieved by electrocoagulation and skin bleeding is arrested by the application of skin towels with Raney clips. With the cutting current, the sternal periosteum is divided from the top of the manubrium to the xiphoid. By sharp dissection, the cephalad 3 to 4 centimeters of the linea alba of the recti abdominis are divided along with the xiphoid process. Through this incision a hemostatic forceps and then a finger may be introduced beneath the lower gladiolus to separate from it the tissues of the anterior mediastinum. Green goiter (blunt) retractors are then inserted at the edges of the recti at the xiphoid, and by means of these the sternum is elevated and, as it is cut, separated. The sternum is then divided smoothly and cleanly with a Luck saw or its equivalent, as shown in Figure 2A. The retractors are advanced behind the saw to elevate and retract the sternal halves. This step is of particular importance as in many of these patients the hypertrophied right ventricle presses against the inner surface of the sternum. With the sternum divided, the transverse manubrial ligament and fibers of the "strap" muscles and their enveloping fascia are divided by scissors in the root of the neck. This should be done in order to provide exposure before attention is turned to hemostasis. At this stage, electrocoagulation of the under surface and ends of the sternal periosteum and thorough waxing of the cut bony surfaces will yield a dry wound.

The phrenoxiphoid ligament and a few fibers of the diaphragm may then be divided and the chest retractor introduced. The Himmelstein hinged retractor has been found very useful for children of all sizes. As the retractor is opened gradually, it may be necessary to increase slightly the dissection of the cervical fascia and diaphragm.

The anterior mediastinal areolar tissue is divided in the midline from the lower thymal border to the diaphragm to expose the pericardium (Fig. 2B). It is not necessary to dissect the left pleural reflection from the pericardium at all. The right pleural reflection must be dissected along the diaphragm occasionally in order to open the pericardium to expose the inferior vena cava. The lower thymal border is identified and dissected by meticulous sharp technique from the adjacent pleurae and pericardium, until the pericardium covering the pulmonary artery and aorta is well exposed. If the thymus is large, it can be split in the midline with very little bleeding. This step allows the respective lobes to fall away.

CANNULATION OF THE INTERNAL MAMMARY ARTERY

The self-containing retractor is removed at this point and either the left or right ster-

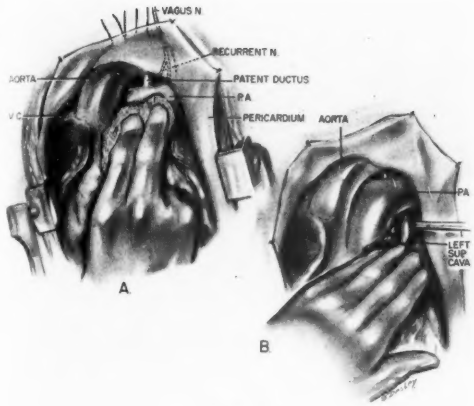

FIG. 4.

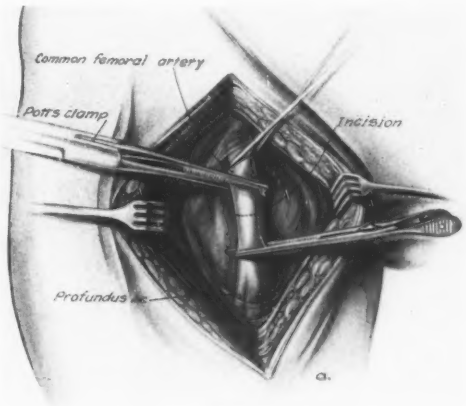

FIG. 5.

FIG. 4. A, The intrapericardial exposure of the ductus arteriosus area is routine prior to bypass in septal defects. By gently depressing and retracting the right ventricle by means of a saline moistened sponge the subaortic area is readily exposed as shown. The recurrent nerve loops around the aorta extrapericardially and thus is not visualized. As a landmark, it may be recalled that the ductus nearly always lies directly opposite to the origin of the left subclavian artery and slightly to the left of the pulmonary artery bifurcation. If the ductus is patent it is divided between suitable vascular clamps. If merely suspected of possible patency it is ligated with a heavy silk ligature before bypass. B, Exposure of left superior cava. This anomaly is routinely searched for and, if large, is cannulated from the right atrium via the coronary sinus. If small, it may be safely occluded without cannulation during bypass.

FIG. 5. Technique of common femoral artery cannulation for cardiac bypass. a, The right or left common femoral artery is exposed by an oblique incision parallel to and slightly below the inguinal ligament. The artery is encircled proximally with a cotton tape and after systemic heparinization vascular clamps are applied as shown. The artery is then incised across half of its diameter with a pair of iris scissors.

nal half is elevated and retracted. The pleura is carefully dissected away from the under surface of the sternum to reveal the internal mammary (Fig. 3A). A suitable polyethylene or teflon tubing is inserted into this vessel routinely in every patient undergoing open heart surgery for a continuous arterial pressure recording. Even in tiny infants a continuous pressure recording may be obtained regularly from this convenient site. Wound hemostasis is rechecked and the retractor reinserted. The pericardium is then picked up and opened in the midline from the diaphragm to the root of the aorta at which point the incision veers to the left along the pulmonary conus and artery to the pericardial reflection on this vessel (Fig. 3A). The edges of the pericardium are picked up with hemostats and the entire pericardial border is electrocoagulated to prevent annoying oozing later from this very vascular structure. Coagulation before incision carries the danger of electrical or heat stimulation of the heart. Occasionally, it is necessary to incise the pericardium on the right parallel to the diaphragm and just above it in order to provide exposure of the inferior vena cava. In this instance the pleura must first be dissected away intact by blunt and sharp dissection. Figure 3B shows the completed exposure.

The inferior vena cava is best approached from within the pericardium by incising the pericardial lining in the groove between it and the left atrium laterally. A long curved hemostat can then be passed behind it and seen through the remaining pericardium medially. The superior cava is easily encircled cardiac to the azygos vein by making a small nick posteriorly over or cardiac to

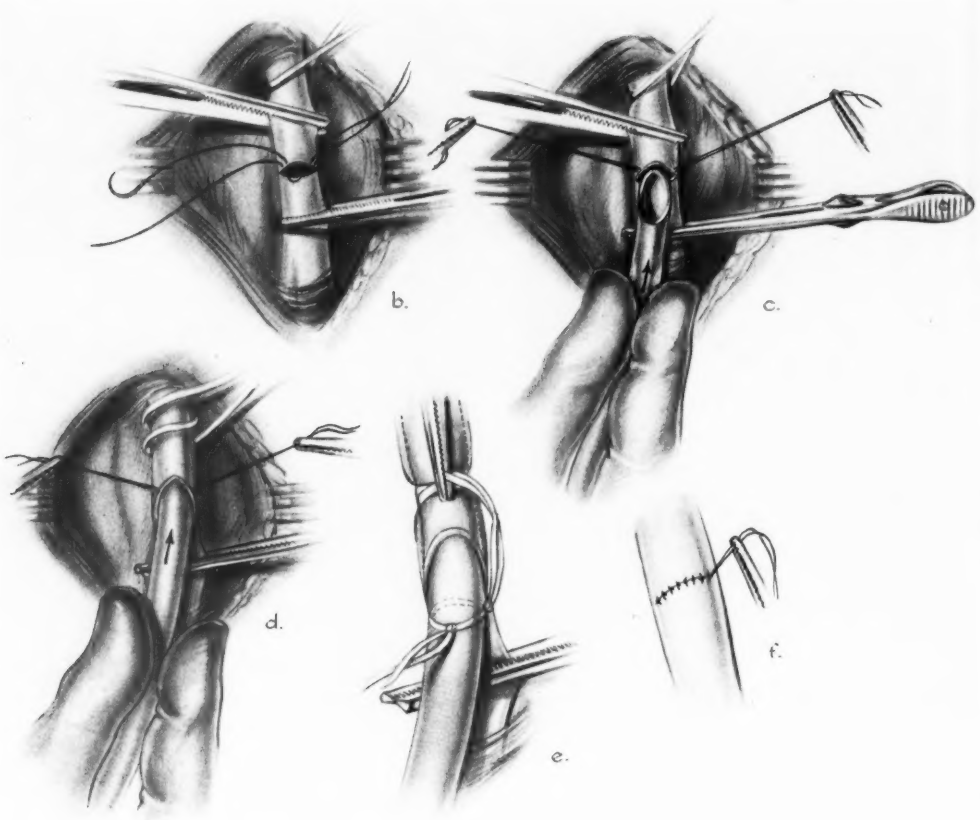

FIG. 6. Technique of common femoral artery cannulation for cardiac bypass (continued). b, Two fine silk (No. 5-0 with swedged needles) stay sutures are placed in a mattress fashion to facilitate gentle traction upon the artery as the beveled catheter with single end opening is introduced. c, The largest catheter that will enter the artery with gentle pushing is selected and just before introduction the plastic catheter is well lubricated with a thin film of sterile mineral oil. d and e, The catheter is introduced 2.5 to 10 centimeters. Since resistance to blood flow is proportional to length, the catheter is trimmed as short as appropriate before insertion. The previously placed cotton tape is passed around the artery again to form a hitch as shown. A moderate degree of tension (enough to indent the plastic slightly) is maintained by clamping the tape with a Rankin forceps. By using a broad tape with care to insure its lying flat against the artery wall, the catheter can be securely held without damage to the arterial intima. Also, the tape is not knotted but clamped for the same reason. The free ends of the tape are then tied a second time around the catheter itself as an additional safeguard. In all perfusions, customarily a flow rate is used that will keep the systemic blood pressure (internal mammary artery cannula) normal (50 to 100 c.c. per kgm. body weight per minute). Utilizing this method of cannulation and the Sigmamotor occlusive pump we have had no difficulty in routinely attaining this objective and dislodgement of the arterial catheter has not occurred. f, After removal of the arterial catheter the artery is carefully repaired using an over and over stitch of No. 6–0 silk. The artery is never left unless there are good pulsations distally. On several occasions it proved expedient to transect the artery completely before repairing it.

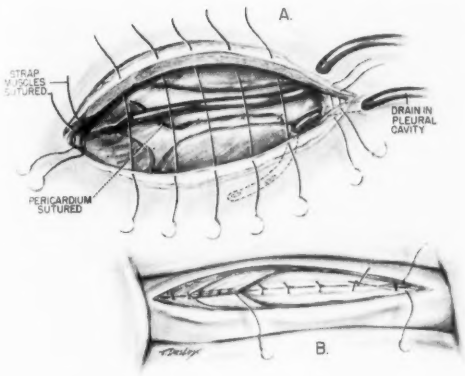

Fig. 7

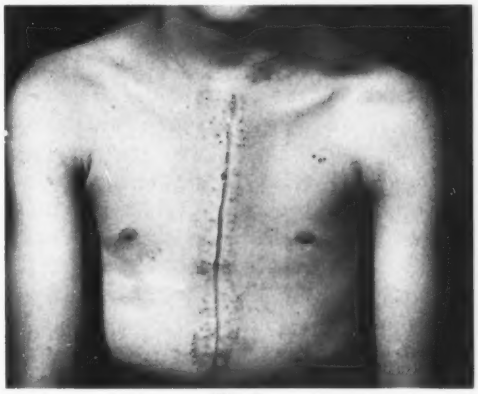

Fig. 8

FIG. 7. Incision ready for closure. A, The pericardium has been loosely approximated. Five stainless steel sutures (No. 25) have been placed through or around the sternum. (In cyanotic patients with a bleeding tendency refer to alternative method of sternal reapproximation described in text.) A plastic catheter is inserted into the mediastinum. If either pleural cavity has been inadvertently entered, it is drained, otherwise not. One or 2 catgut stitches reapproximate the strap muscles and fine silk unites the linea alba inferiorly. B, The sternal halves have been firmly approximated and the remaining layers are closed.

FIG. 8. The appearance of the midline incision 14 days postoperatively in an 8 year old patient who had a ruptured aneurysm of a sinus of Valsalva combined with isolated infundibular pulmonic stenosis both of which were corrected during the course of a 42 minute interval of bypass.

the right pulmonary artery. The aorta is then looped in the usual fashion by separation medially from the pulmonary artery. The pericardium between the aorta and pulmonary artery is then opened and the subaortic space is explored to eliminate the possibility of a patent ductus arteriosus (Fig. 4A) or left superior cava (Fig. 4B). The patient is then heparinized and the femoral artery catheter is inserted as indicated in Figures 5 and 6. The superior and inferior cavae are then cannulated by means of separate plastic catheters inserted through purse-stringed portions of the right atrial wall as previously described (4). Rather than tying this purse-string suture around the catheter to effect hemostasis, the same objective may be accomplished by threading the two ends of the purse-string stitch through a narrow bore rubber catheter, and then cross-clamping with a hemostat after pulling them up snugly. This method allows the same stitch to be tied when the catheters are removed.

Upon completion of the intracardiac procedure, removal of the cannulas, and restoration of normal blood coagulability, all areas of dissection are again carefully inspected and any persistent oozing is coagulated. The femoral arteriotomy is repaired with fine (No. 6-0) silk at this stage (Fig. 6). When the cardiac performance is considered satisfactory the pericardium is loosely reapproximated with interrupted silk sutures. The mammary catheter is removed and after a final check for bleeding the sternum is reapproximated as follows: First a plastic thoracic drainage catheter of appropriate size is laid in the anterior mediastinum with its tip beneath the thymus and its end brought out through a subcutaneous tunnel over the abdomen below the chest wound. If either pleural space has been inadvertently entered, a second chest tube is inserted into the space and the lower end is brought out parallel to the mediastinal tube (Fig. 6).

Two or 3 interrupted No. 0 chromic catgut sutures are placed in the "strap" muscles and cervical fascia but not tied until the sternum has been approximated (Fig. 7). Five to 7 single sutures of No. 23 or 25 single strand stainless steel wire are then brought

out through the sternum and when all are placed, the sternum is pulled together and the wire ends are secured by twisting. The suture holes in the sternum may be a site for postoperative bleeding, especially in patients with a hyperplastic sternal marrow and clotting deficiencies associated with cyanosis. To obviate this problem, a useful alternative method for sternal approximation is effected by placing 3 to 5 pairs of mattress stitches of wire through each sternal half, and then pulling the sternum together by twisting these together across the midline. Before being inserted through the sternum the loop of each mattress stitch is buttressed first by passage of the respective arms through a pledget of compressed polyvinyl sponge which, when pulled up against the undersurface of the sternum, effectively prevents any bleeding into the chest from the stitch holes.

The recti abdominis are carefully reapproximated with No. 3-0 silk interrupted sutures, and the chromic sutures in the neck are tied. The sternal periosteum and deep fascia are closed with interrupted sutures of No. 2-0 chromic catgut and the subcutaneous tissue with a running suture of No. 34 steel wire or fine catgut followed by standard skin closure with No. 5-0 silk. The chest tube is immediately attached to chest suction at about 20 centimeters of water as soon as inserted and may usually be removed by the second day. Figure 7A shows the incision ready for closure and Figure 7B with the sternal halves approximated. Primary healing has occurred in all but 1 of these patients (Fig. 8).

In conclusion, we have found the median sternotomy a valuable adjuvant to the surgery of ventricular septal defects, various forms of pulmonic stenosis, ruptured aneurysms of sinus of Valsalva, or aortic valve disease and feel confident that it has contributed importantly to the reduction of operative risk in patients with severe pulmonary hypertension and in those who constitute poorer risks for other reasons. It has also proved particularly valuable in lessening abnormal bleeding problems in the deeply cyanotic individuals with grossly deranged clotting mechanisms preoperatively who are in need of open heart procedures. For the many patients with extensive adhesions from previous palliative surgery who are to undergo subsequent curative procedures, the midline sternotomy has proved to be a boon.

In the 200 heparinized patients upon whom this incision was utilized for open heart procedures employing the disposable helix reservoir (bubble) oxygenator and Sigmamotor pump, there has not been a single instance of abnormal postoperative bleeding nor has any patient required reopening of the chest to control bleeding. It is perhaps obvious that careful perfusion technique, vigilant hemostasis facilitated by use of the electrocautery and the superior antiheparin agent polybrene have, in addition to this incision, all contributed to the complete freedom from bleeding problems.

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INCIDENCE OF METASTASIS IN THE INTERNAL MAMMARY CHAIN IN OPERABLE CANCER OF THE BREAST

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THE ACCEPTED surgical treatment of cancer of the breast is radical mastectomy based on the assumption that cancer cells spread only via the axillary lymph vessels. However, pathologic studies by several workers confirm the fact that supraclavicular metastases are almost always secondary to invasion of the axillary nodes, whereas metastases to the internal mammary chain sometimes precede axillary invasion. These findings provide one reason for the failure of the standard radical mastectomy.

Efforts to control this secondary lymphatic drainage of the breast have been made by monoblock excision of the internal mammary lymph nodes with the breast and the contents of the axilla.

MATERIAL

During the 3 year period from September 1954 to September 1957, 269 radical mastectomies for cancer were performed in the Instituto Nacional de Enfermedades Neoplasicas, of which 261 were performed in the Breast, Bone, and Mixed Tumors Department under the control of the same surgical team. Of these patients, 258 were subjected to resection of the internal mammary chain along with the breast and contents of the axilla. This was not performed in 3 cases, one because of advanced pulmonary tuberculosis with low vital capacity, another because of technical difficulties, and the third because of the opposition of the patient's relatives.

The first 250 consecutive cases have been tabulated for study. The material, therefore, consists of an unselected series of patients, both private and free, almost all of whom, without consideration of their age and the location of the tumor in the breast, underwent resection of the internal mammary chain.

The median age was 50.1 years, the youngest patient being 22 years old and the oldest 82; 97 (38.4 per cent) were private patients, and 153 (61.6 per cent) were free. The criterion of operability was that established by Haagensen and Stout.

SURGICAL TECHNIQUE

The incision employed is the same as that used for a typical radical mastectomy. Depending on the location of the tumor in the breast, generally one of three incisions is used, the Halsted-Meyer, the Stewart, or the Greenough incision.

First, dissection of the outer flap is performed; next the internal flap is dissected as far as the opposite sternal border. Then the internal mammary chain is approached by separating the pectoralis major muscle from its upper clavicular and sternal end, thus exposing the inner portion of the first intercostal space. The external intercostal muscle is resected immediately below the lower edge of the first rib, and when this is separated with a gubias bone forceps the lower part of the first rib is resected at its sternal end including part of the costosternal junction. This is considered a very useful maneuver, since it enables one to widen the first intercostal space and ligate the internal mammary vessels practically at the upper edge of the first rib, and it facilitates the ample resection of the first intercostal space

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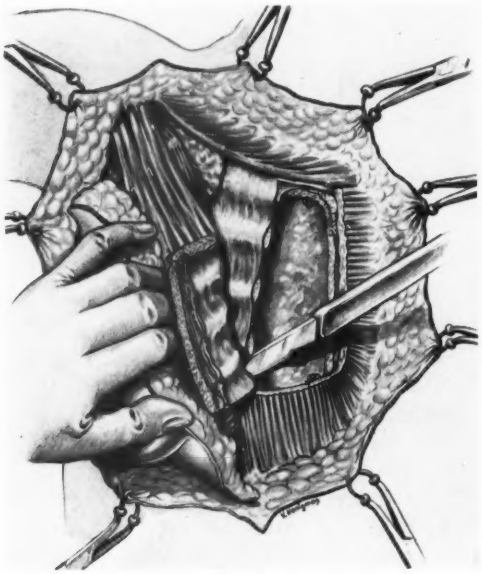

FIG. 1.

FIG. 2.

FIG. 1. Illustration showing the excision of a block of chest wall in continuity with the breast and together with the underlying internal mammary vessels and lymph nodes, leaving the pleura intact. The resection of the lower part of the first rib can be observed.

FIG. 2. A few days after the operation showing that the defect in the chest wall may be seen when the patient takes a deep breath.

with its contents. Once the mammary vessels have been ligated, the pleura is separated by introducing the finger downward along the length of the sternum, and then, with Lebsche's sternal knife, the border of the sternum is sectioned as far as the fourth intercostal space which is resected in its entirety. Thus it is possible to lift this portion of the costal wall outward and gently to detach the pleura until it is freed as far as the outer cartilaginous portion of the second, third, and fourth ribs, to resect the ribs at the level of their osteocartilaginous junction, and to leave them joined to the pectoralis major muscle (Fig. 1).

The major and minor pectoralis muscles are separated from the thoracic wall, and dissection of the axilla is performed as in the classic radical mastectomy.

In this way, it is possible to perform a resection en bloc and in continuity of the breast, the contents of the axilla, and the internal mammary chain in an extrapleural manner. Sometimes, the pleura is torn for a short length during the separation, but this can be repaired with separate stitches. If the tear is so great that it cannot be repaired, resection of the pleura is performed and a fascia lata graft, such as described by Urban, is used (8). This has happened only rarely, and never in the last 160 cases.

The operation described has not been followed by greater morbidity than the typical radical mastectomy. The patient usually leaves the hospital on the seventh or eighth postoperative day.

The defectiveness of the costal wall can be noticed when the patient takes a deep breath. However, this defect tends to diminish after a few months, probably by fibrosis of the pleura, which provides good support (Fig. 2).

RESULTS

It has been established that the incidence of metastases to the internal mammary chain is more frequent in tumors located in the inner half of the breast. With a view to determine the exact location of the tumor and not to depend on its description, in each case the site of the tumor was marked on a diagram later used for the tabulation.

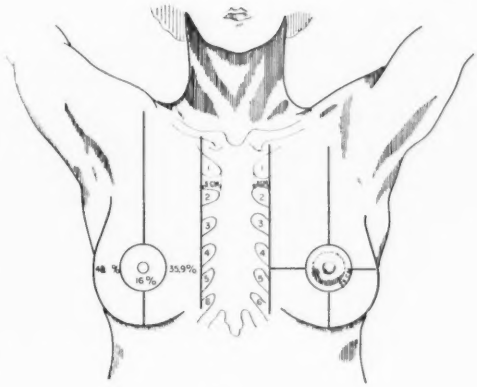

FIG. 3.

FIG. 3. Distribution of 248 primary tumors (tumors not palpable in 2 cases). Diagram used to mark the site of the tumor in each case. The distribution of the tumors in different sectors of the breast is shown on the right breast.

FIG. 4. Distribution of the internal mammary lymph nodes in 129 cases. On the right, the total number of lymph nodes medial and lateral to the internal mammary vessels; on the left, the distribution of the lymph node invaded.

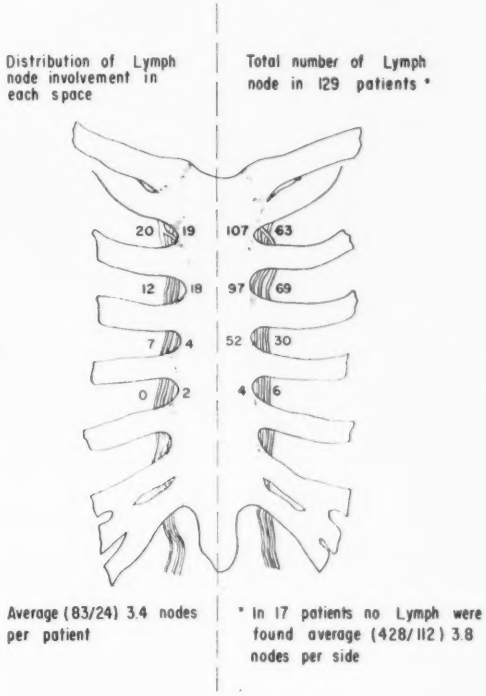

FIG. 4.

As shown in Figure 3, 48 per cent of the tumors were located in the outer quadrants, 16 per cent in the central area, and 35.9 per cent in the inner quadrants.

Our operative findings have been summarized in Table I.

Of the 250 patients operated on, 152, or 60.8 per cent, had metastases to the axilla, which means a high incidence of axillary metastases. Only 36.8 per cent of the patients were free of metastases. In 19.2 per cent there was metastases to the axilla and the internal mammary chain, and in 2.4 per cent to the internal mammary chain only, which is an incidence of 21.6 per cent of metastases to the internal mammary chain in this series of unselected patients.

The incidence of metastases to the internal mammary chain in our series is lower than in those of Urban (8), Wyatt, Sugarbaker, and Stanton, and Handley, which fact is probably due to the selection of material made by these authors who limited resection of the internal mammary chain to patients with lesions located in the inner quadrants. The present material is comprised of a series of unselected patients having an operable cancer of the breast.

It has been established that the incidence of metastases to the internal mammary chain is more frequent in tumors located in the inner half of the breast. In this series, when the tumor was located in the inner half of the breast, 29.2 per cent had metastases; when it was located in the central portion, 24.3 per cent; and when located in the outer half, the incidence of metastases was 15.2 per cent.

Although it is clearly demonstrated that there is a greater incidence of metastases in lesions located in the inner and central portions of the breast, the percentage of 15.2 per cent for external lesions is not to be disregarded and does not justify the confining

TABLE I.—INCIDENCE OF LYMPH NODE METASTASES IN RELATION TO SITE OF PRIMARY TUMOR

	Inner quadrant		*Central*		*Outer quadrant*		*Total*	*Per cent*	
All nodes free	37		15*		40		92	36.8	
Axillary nodes alone	26		16†		60		104‡	41.6	60.8
Axillary and internal mammary nodes invaded	22	29.2	10	24.3	16	15.2	48	19.2	
Internal mammary nodes invaded alone	4		0		2		6	2.4	21.6
Total	89		41		118		250‡	100	

*4 cases of Paget's disease.
†1 case of Paget's disease.
‡In 2 cases the tumor was not palpable.

of this type of operation only to lesions located in the inner and central quadrants.

In the group of patients with axillary metastases, the incidence of involvement of the internal mammary chain is very much higher, 31.5 per cent, which means that one-third of the patients with metastases to the axilla also present metastases to the internal mammary chain.

In this group with axillary metastases, if the incidence of metastases to the internal mammary chain is analyzed in relation to the location of the tumor, it is found that when the tumor is located in the inner half, the incidence of metastases is 45.8 per cent, and when it is located in the central portion of the breast the incidence is 38.4 per cent. When the tumor is located in the outer half of the breast, the incidence drops to 21 per cent (Table II).

When there is no axillary involvement, the possibility of metastases to the internal mammary chain is 6.1 per cent, rising to 9.7 per cent when the tumor is located in the inner portion of the breast (Table II). The incidence of involvement of the internal mammary chain in relation to the extent of the metastases in the axilla is more frequent the larger the axillary lesion. Table III shows that the metastases rate of the internal mammary chain increases from 16.6 per cent, when level I is affected, to 39.7 per cent, when level III is involved.

TABLE II.—INCIDENCE OF INVASION OF INTERNAL MAMMARY NODES IN RELATION TO SITE OF PRIMARY TUMOR AND AXILLARY INVOLVEMENT

	Inner quadrants	*Central*	*Outer quadrants*	*Total*
Axillary and internal mammary nodes invaded	22	10	16	48
No. of cases with axillary nodes invaded	48	26	76	152*
Per cent	45.8	38.4	21	31.5
Internal mammary nodes invaded alone	4	..	2	6
No. of cases without axillary node invasion	41	15	42	98
Per cent	9.7	..	4.7	6.1

*In 2 cases the tumor was not palpable.

DISTRIBUTION OF LYMPH NODES AND METASTASES IN INTERCOSTAL SPACES

The study of the involvement of the internal mammary chain covered the first 4 intercostal spaces. In 8 of the 54 cases of metastases to the internal mammary chain, there was involvement of 3 or more spaces.

In Table IV, the involvement of the several intercostal spaces is shown, and a greater incidence is noticed in the first and second intercostal spaces. This observation proves that the lymphatics of the internal mammary chain drain mainly into the lymph glands of the first 3 intercostal spaces, and occasionally into the fourth intercostal space, and that therefore the resection of the lymph glands of the first 4 intercostal spaces can be judged an adequate eradication of this secondary filter of the lymphatic drainage of the breast. When the lymph glands of the lower intercostal spaces are invaded, this is probably due to a retrograde permeation.

The first intercostal space was invaded in 37 cases, or 68.5 per cent of the present series. This is a higher incidence than the 44 per cent in Margottini's series. He found a greater involvement at the level of the sec-

TABLE III.—INCIDENCE OF INTERNAL MAMMARY NODE INVOLVEMENT AND AXILLARY METASTASES EXTENSION

	Level I	*Level II*	*Level III*	*Total*
No. of cases with axillary metastases	48	21	83	152
Internal mammary node invasion	8	7	33	48
Per cent	16.6	33.3	39.7	31.5

TABLE IV.—FREQUENCY OF LYMPH NODE INVOLVEMENT IN EACH INTERCOSTAL SPACE IN 54 CASES

Intercostal space	*No.*	*Per cent*
Invasion of first space	37	68.5
Invasion of second space	28	51.8
Invasion of third space	16	29.6
Invasion of fourth space	3	5.5
Invasion of first space only	13	
Invasion of second space only	8	
Invasion of third space only	3	
Invasion of fourth space only	2	

In 8 cases, invasion of 3 or more spaces.
84 spaces invaded in 54 cases.

ond intercostal space. Urban (9) also found a greater involvement in the second and in the third intercostal spaces than in the first.

In the present series, the greater incidence in the first intercostal space is due to the resection of the first rib permitting ligation of the internal mammary vessels almost at the upper edge of the first rib, and excision en bloc of the whole of the first intercostal space. The greater frequency of metastases, be it multiple or simple, in the first intercostal space, indicates the importance of a complete resection of the first intercostal space which is only possible when part of the first rib is resected.

In order to ascertain the frequency, extent, and distribution of the lymph glands of the internal mammary chain in relation to the internal mammary vessels, a careful dissection of the lymph glands of the internal mammary chain was performed in 129 consecutive cases, and notice was made not only of the number of glands in each space but also of their position in relation to the mammary vessels. In addition, histologic verification was made when it was not possible to locate glands macroscopically, to do this the space was divided into two parts with the mammary vessels for axis. In this way, it was possible to detect glands of even less than 5 millimeters.

In Figure 4 on the right, the total number of glands may be observed within and without the mammary vessels at the level of each space, showing a predominance of glands inside the internal mammary vessels. An average of 3.8 glands per side in the 4 spaces was observed, which agrees with the number found in autopsy material by other authors, as Ju who found 3.1, Soerensen 3.5, Stibbe 4.2, with the exception of Abrao and Da Silva who found an average of 8.9 and 7.2 glands per side.

On the left side of Figure 4 are shown the number and the distribution of the glands that were positive for metastases, and it may be seen that they were evenly distributed within and without the internal mammary vessels. This fact is important, because if the mammary vessels are generally situated half a centimeter from the sternal border and often on the border itself, then to ensure the extirpation of all the glands, the resection of the edge of the sternum is necessary.

DISCUSSION AND CONCLUSIONS

Whether or not radical mastectomy with resection of the internal mammary chain improves the results in the treatment of cancer of the breast cannot at present be affirmed. However, the operation is established on a reasonable basis that can be verified, without greater morbidity or mortality than the classical radical mastectomy. In a series of 250 patients, the operative mortality was less than 1 per cent. The high incidence of metastases to the internal mammary chain in tumors located in the outer half of the breast (15.2 per cent) justifies the extension of this type of operation to all mammary tumors, whatever their location.

In this series, the first intercostal space has been the one most frequently involved. In my opinion, this greater frequency is due to the complete excision of the first space, which is achieved by resecting the lower half of the first rib, as suggested also by Handley and collaborators.

This operation is still in the experimental stage, and therefore its employment should be limited to specialized centers handling a great deal of clinical material.

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THE MISUSE OF ANTIBACTERIALS IN INGUINAL HERNIORRHAPHY

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THE DEVELOPMENT of antibiotic-resistant bacteria, which is one of the chief causes of hospital infections presently causing such grave concern, has been hastened by the unnecessary use of antibiotics in patients who have had no proved infection. Although frequent statements have been made deploring the use of antibiotics in such conditions, no reports have been published showing conclusively the extent to which antibiotics have been misused in a group of community hospitals in conditions for which these drugs clearly were not indicated.

We now have available for the first time data which demonstrate the misuse of the antibacterials (antibiotics and sulfonamides) in one disease condition which is ideally suited to be a testing ground for the justification of the use of these drugs. Simple or uncomplicated inguinal hernia, in which there is no incarceration or strangulation of the intestine or other abdominal contents, is one condition in which infection is not expected to occur after the surgical repair of the hernia, provided that adequate aseptic surgical technique has been followed and proper selection and preparation of the patient have been observed. There is nothing inherent in a simple inguinal hernia which requires or justifies the prophylactic use of antibacterials; and the use of these drugs should properly be reserved for the relatively few cases of simple inguinal hernia in which a preoperative infection must be eradicated before surgery, or in which an established postoperative infection should be treated with the indicated drug.

This is a critique of the use of antibacterials in 1,536 inguinal herniorrhaphies performed in 24 community hospitals located in 7 states, participating in the Medical Audit Program[1], developed by the American College of Surgeons and the Commission on Professional and Hospital Activities.[2] Each of these 24 hospitals is accredited by the Joint Commission on Accreditation of Hospitals; 9 of this group are approved for internship training by the American Medical Association or for graduate training in surgery by the Conference Committee on Graduate Training in Surgery. In short, this group of hospitals is above average in its attempts to observe high standards of patient care. This series of operations is composed of consecutive patients with both simple and complicated hernias submitted to operation during the year 1957. The evaluations of the patients were done by the medical staff of each hospital during the second quarter of 1958, and their impressions, which were recorded on standard Medical Audit check sheets, have been subsequently transferred to punched cards and processed by business machines in the central offices of the Commission. Analysis of the resultant statistics provides the basis of this critique.

Figure 1 shows the percentage of these 1,536 inguinal herniorrhaphy patients given antibacterials in each of the 24 hospitals. For purposes of comparison, the hospitals are grouped according to size. From this figure it is obvious that there is wide variation between hospitals in the use of antibacterials as part of the treatment of patients submitted to inguinal herniorrhaphy; the range extends from 100 to 9.2 per cent of the

[1]Supported by grants from the W. K. Kellogg Foundation, Battle Creek, Michigan.

[2]Ann Arbor, Michigan—Sponsored by the American College of Physicians, the American College of Surgeons, the American Hospital Association, and the Southwestern Michigan Hospital Council.

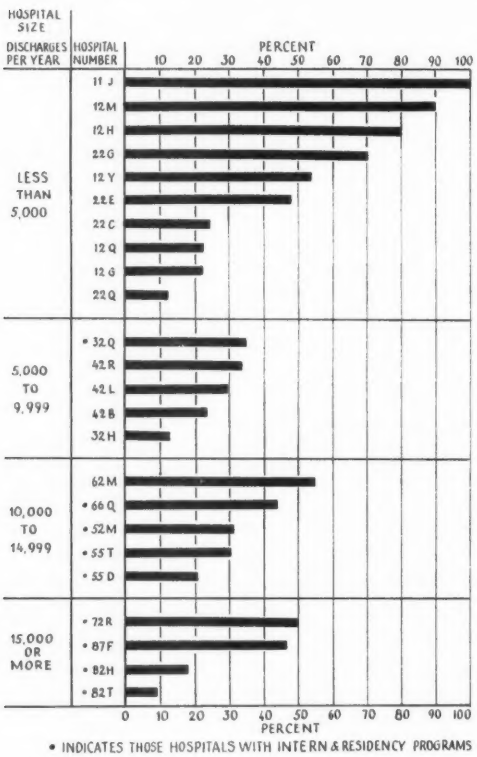

FIG. 1. Percentage of inguinal herniorrhaphy patients given antibacterials, by hospital.

patients undergoing surgery. It is also apparent that the larger hospitals, and those with intern and residency training programs, do not, as a group, differ significantly from individual smaller hospitals in the percentage of patients who receive antibacterials. This observation is of considerable interest, for all too frequently the assumption is proclaimed that "large teaching centers" practice a better brand of medicine by virtue of size, superiority of professional staff qualifications, and the presence of graduate training programs.

Table I shows "when" the antibacterials were used in these 1,536 inguinal herniorrhaphies. One fact is significant: 38.2 per cent of all patients with simple inguinal hernias submitted to surgical repair received antibacterials at some time during

TABLE I.—USE OF ANTIBACTERIALS ACCORDING TO DIAGNOSIS

	Simple		*Complicated*		
Antibacterials	*No.*	*Per cent*	*No.*	*Per cent*	*Total*
With	569	38.2	24	52.2	593
Without	921	61.8	22	47.8	943
Total	1490	100.0	46	100.0	1536

TABLE II.—PATIENTS WITH ANTIBACTERIALS, ACCORDING TO DIAGNOSIS AND REASON FOR ANTIBACTERIAL USE

	Simple		*Complicated*		*Total*	
Reason	*No.*	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Prophylactic	476	84	20	83	496	84
To control infection	84	15	3	13	87	15
Both	9	1	1	4	10	1
Total	569	100	24	100	593	100

hospitalization. As it is not probable that such a large percentage of these patients would have a proved infection which required treatment with drugs, the supposition may be made that many of these patients received antibacterials for prophylactic purposes. It is also of interest that only 52.2 per cent of patients with complicated inguinal hernias, those with incarceration or strangulation of intestine or other abdominal contents, received antibacterials. The complicated hernias are a group in which contamination and infection are frequent and in which prophylactic use might be justified in a high percentage of cases. Yet the difference in percentage of use in these two groups of this series is not marked.

Table II shows "why" the antibacterials were used in this series. It is immediately apparent that our supposition concerning prophylactic use of the antibacterials was correct in that 84 per cent of the patients with simple hernias received these drugs for that purpose; this figure is almost identical with the percentage receiving antibacterials (83 per cent) in complicated hernias in which the possibility of infection is greater.

Table III lists "what" antibacterials were used in the treatment of these patients undergoing inguinal herniorrhaphy. Penicillin, streptomycin, and the tetracyclines were overwhelming favorites, and all other antibacterials were used infrequently. Yet

TABLE III.—ANTIBACTERIALS GIVEN ACCORDING TO DIAGNOSIS

	Simple		Complicated	
Antibacterials	*No.*	*Per cent*	*No.*	*Per cent*
Penicillin	453	79.6	21	87.5
Streptomycin	255	44.8	12	50.0
Chloromycetin	21	3.7	1	4.2
Tetracyclines	143	25.1	5	20.8
Sulfonamides	25	4.4	2	8.3
Other	15	2.6	1	4.2
Total patients	569	*	24	*

*These columns will not total 100 per cent because of multiple use of antibacterials.

TABLE IV.—ANTIBACTERIALS USED IN 593 PATIENTS

		Combination with one other drug				
Drug	*Alone*	*Strepto-mycin*	*Chloro-mycetin*	*Tetracy-clines*	*Sulfona-mides*	*Other*
Penicillin	197	204	3	16	7	1
Streptomycin	1	—	2		1	
Chloromycetin	7	2	—	2		
Tetracyclines	85		2	—	1	3
Sulfonamides	10	1		1	—	1
Other	5			3	1	—
Penicillin and streptomycin	204	—	4	33	4	1

943 patients received no antibacterials.
5 patients received other multiple combinations.

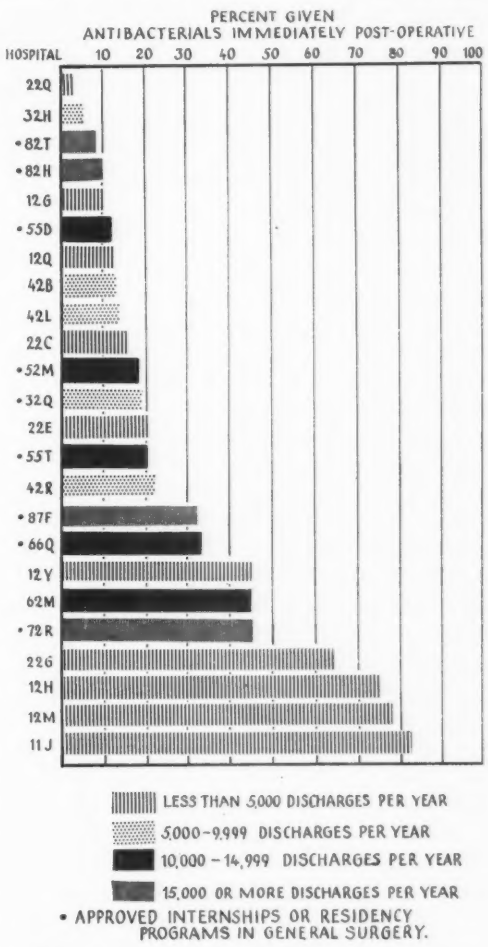

FIG. 2. Unnecessary antibacterial use among uncomplicated inguinal hernia patients, by hospital.

the recent literature indicates that the majority of the strains of staphylococci now encountered in hospital cross infections in the United States are resistant to penicillin, streptomycin, and the tetracyclines, and these drugs would not be expected to be of therapeutic value in infections caused by those bacteria.

Table IV shows the combination of antibacterials used. That streptomycin was used almost entirely in combination with penicillin is probably due to the availability of this combination commercially for parenteral administration.

Table V presents two significant facts: The first is that the physicians who evaluated these patients undergoing inguinal herniorrhaphy believed that 72, or 15 per cent, of the 496 patients receiving antibacterials prophylactically should not have been given these drugs for this purpose. Although this percentage of criticism of prophylactic use is considerably less than will be shown to be indicated, the very fact that these physicians were willing to criticize the care given by their colleagues is an indication that physicians will evaluate critically the care given by other physicians if a practicable mechanism such as the College's Medical Audit method is available. In passing, note should also be made that in only 2 cases were the antibacterials judged to have been indicated but withheld.

The second fact of importance in Table V is that there were 3 times as many postoperative infections, either local wound or of other sites, in the group receiving antibacterials as there were in the group not

TABLE V.—REVIEWERS' CRITICISM OF ANTIBACTERIAL USAGE, AND NUMBER OF POSTOPERATIVE INFECTIONS OCCURRING, ACCORDING TO REASON FOR ANTIBACTERIALS

Reason for antibacterials	*Total No. of cases*	*Reviewers' criticism of usage of antibacterials*				*Postoperative infections occurring*	
		Too little given	*Too much given*	*Given inappropriately*	*Improperly withheld*	*No.*	*Per cent*
None given	943	0	0	0	2	12	1.3
Prophylactic	496	1	3	72(15 per cent)	0	20	4.0
To control infection	87	0	4	5	0	45	51.7
Both prophylactic and control	10	0	0	0	0	6	60.0
Totals	1,536	1	7	77	2	83	5.4

receiving these drugs. The reasons for this are not apparent; perhaps it may have been due to a greater number of poor risk patients in the group receiving prophylactic antibacterials; but, on the other hand, it is possible that those surgeons using prophylactic antibacterials were not as careful of their aseptic surgical techniques and relied too heavily on the antibacterials.

Figure 2 presents my rating of these 24 hospitals based on the frequency with which antibacterials were used unnecessarily for prophylaxis in each hospital. These statistics for prophylactic use differ from the opinions of the reviewing physicians as presented in Table V, and were obtained as follows: the 596 patients with simple inguinal hernias receiving antibacterials were analyzed to find out when the initial dose of antibacterial was given to each patient. Those receiving antibacterials preoperatively were judged to have received the drugs justifiably to eradicate a preoperative infection, although it is admitted that a certain percentage of such patients might have received preoperative antibacterials as a prophylactic measure. Those receiving antibacterials after evidence of postoperative infection had occurred were likewise classed as justified. The group receiving antibacterials for the first time as an immediate postoperative order, on the other hand, were judged as receiving the drugs prophylactically and hence unnecessarily. A comparison of the number in this category with the total number of patients operated upon for simple inguinal hernias in each hospital gave an arbitrary rating which indicates in a descending order of excellence the misuse of antibacterials by hospitals. It is evident that a small hospital with less than 5,000 discharges per year received the highest rating for using antibacterials the most intelligently. The ratings of the "teaching centers" are apparent.

From the field of fact to the realm of fancy is but a short step, and in this particular study, speculation based on facts provides some interesting estimates of economic waste due to the unnecessary administration of antibacterials in inguinal herniorrhaphy. From our statistical studies, as revealed in Figure 2, it was found that 421 patients or 74 per cent of the 569 patients with simple inguinal hernias receiving antibacterials received these drugs needlessly, that is, the first dose immediately postoperatively. It is known that patients in this series received antibacterials on the average for 5.1 days. If these 421 patients received the minimum of 1 dose a day for 5.1 days, then they received a total of 2,147 unnecessary doses during hospitalization, or an average of 89 unnecessary doses per hospital in this study of inguinal herniorrhaphy. If the average cost to the patient for 1 dose of antibacterials is set at the low figure of 50 cents, then the average unnecessary cost for antibacterials to patients undergoing repair of simple inguinal hernias in each hospital was $44.50. If this same minimum waste is projected into the 5,546 general hospitals reported in the 1958 Guide Issue of the American Hospital Association, then there would be a minimum unnecessary cost of about $247,000 to patients undergoing inguinal herniorrhaphy alone in hospitals in the United States.

As for the waste of nurses' time in giving these unnecessary doses of antibacterials in inguinal herniorrhaphy, if the very modest estimate of 3 minutes per dose were established as the time required for a nurse to give 1 dose of antibacterials, then an average of 4.5 hours was wasted in each of the 24 hospitals giving antibacterials for prophylaxis in inguinal herniorrhaphy. If these figures were projected into 5,546 general hospitals, this would mean a loss of approximately 25,000 nurse hours spent in administering needless antibacterials for this 1 operation only during the period of 1 year.

As a matter of fact, these estimates of $247,000 of wasted money and 25,000 wasted nurse hours involved in the dispensing of prophylactic antibacterials needlessly to patients undergoing inguinal herniorrhaphy in the United States are probably conservative. It is our personal observation from numerous audits in hospitals in all sections of the country that the prophylactic use of antibacterials in surgery has become almost a routine procedure.

SUMMARY

A critique of the misuse of antibacterials in a series of 1,536 inguinal herniorrhaphies done in 24 hospitals located in 7 states has been presented. This study shows that 74 per cent of the patients given antibacterials in conjunction with the surgical repair of simple inguinal hernias were given these drugs needlessly, that is for prophylaxis. Moreover, the drugs given in most cases, penicillin, streptomycin, and the tetracyclines, are probably without therapeutic value in the prevention of staphylococcal infections which are being encountered presently in hospitals. Such misuse of antibacterials not only exposes patients needlessly to the dangers of serious and even fatal reactions, but it also wastes much money and nurses' time.

EARLY ELECTROLYTE AND COLLOID THERAPY IN BURNED INFANTS AND CHILDREN

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IN A PREVIOUS ARTICLE (1), pilot studies in the early treatment of burns in infants and children were described. These studies were undertaken in 1954 because of uncertain and, at times, confusing results with present day formulas for burn treatment.

Authors who present formulas for early treatment universally conclude that these are only the basic general needs and too many details are omitted which are essential to know in order to ensure adequate early therapy. At the beginning of the present investigation, it was concluded that the more complicated the treatment was made, the greater was the likelihood of serious mistakes on the part of resident and nursing personnel.

To understand the rationale in the present method of treatment, some elemental physiopathology that follows a burn must be appreciated. Losses of water, electrolytes, and plasma-like fluid occur not only from the weeping burn surface but into the wound edema in and surrounding the burn. These losses occur rapidly. King estimates that 90 per cent of the wound edema occurs in the first hour in untreated animals. In treated patients, due to increased capillary permeability, these losses continue into the burned wound. With only moderate early replacement therapy, continued sequestration occurs at the expense of the blood volume, with resultant decreased blood volume, hyponatremia, dehydration, hypotension, and anoxia to the body cells. The most important reflection of inadequate early treatment is oliguria which, if allowed to persist over several hours, must in many more cases than is realized, result in kidney damage. In the realization that the damaged extracellular space must be filled to near capacity before body fluid will be adequate for correction of oliguria, fluids of rather high electrolyte content are given rapidly immediately after admission to the hospital. An attempt is made to secure an adequate urinary output within 3 hours after admission. Fifty cubic centimeters of urine hourly in the adult and 25 cubic centimeters in the child are believed to constitute an optimal output.

It has been shown (4) that the plasma exudate in the burn edema wound is one-half to two-thirds that of blood plasma, and this colloid loss, if not replaced, will cause decreased blood volume and shock. No matter how rapidly electrolytes are administered early, oliguria will persist as long as the kidney filtration pressure is greatly below normal.

It has been observed by the author that burn stress should give the patient a high normal blood pressure provided adequate treatment is given. Low normal blood pressure readings with concomitant renal vasoconstriction and oliguria indicate inadequate colloid therapy.

Since the colloid loss is mainly in the form of plasma loss and not blood cell destruction, it is believed that stored plasma is the colloid of choice in burn treatment.

As the earliest and most rapid loss is water with a high electrolyte content, the initial replacement solution of choice should be 5 per cent glucose in Ringer's lactate, and should be given rapidly within the first 3 hours until an adequate urinary output has been established. Following this initial treatment, a more hypotonic solution (or one

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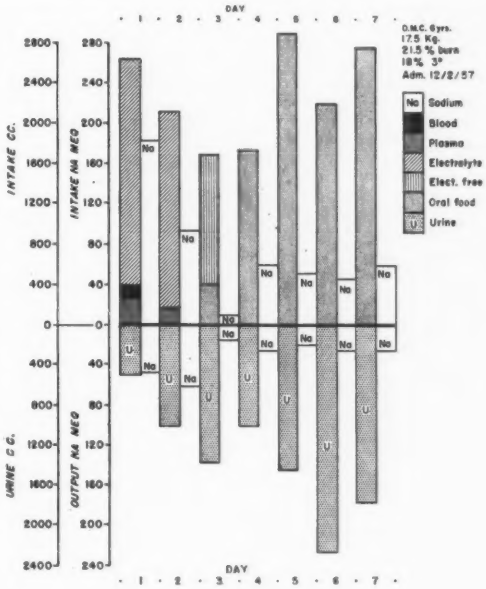
containing less sodium) should be administered. To mix a solution containing less sodium than Ringer's lactate, merely pour out a certain amount from a bottle containing 5 per cent glucose in Ringer's lactate and replace this amount with 5 per cent glucose in water. The problem on our metabolic service has been to determine the optimal electrolyte concentration to use after initial stress therapy, and the proper time thereafter to reduce electrolyte content, according to the extent of the burn. Conclusions drawn have been the result of many tests with varying concentrations of electrolytes, observing clinical course, and performing strict intake and output studies during a week of treatment.

To estimate colloid replacement, the formula—kilograms of body weight times percentage of third degree or deep second degree burn times 1 equals the amount of colloid needed in the first 24 hours—is used (limit estimate to a 50 per cent burn). One-half of the amount is administered in the second 24 hours. All of the early colloid replacement is in the form of stored plasma. A small quantity of blood is usually given at the end of the first 24 hours.

Plasma should be given within the first 3 to 4 hours of treatment, prophylactically, and at any other time that the blood pressure falls from a normotensive range, particularly if there is oliguria with a seeming adequate electrolyte administration.

Schiffer and Crews have theorized that early establishment of hydration and replacement of electrolyte losses are important in preventing an abnormal hormonal pattern which, if allowed to continue, may produce antidiuretic and sodium retention factors which may be extremely difficult to control and treat intelligently once they have been established. Following this reasoning, to prevent abnormal hormonal influences, fluids which contain electrolytes are given continuously during the first 48 hours. By combining the solutions, the sodium concentrations are made less during the periods of treatment when it is believed that less sodium



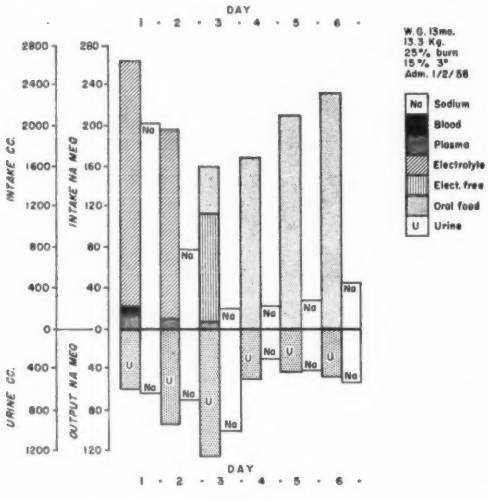
CHEMISTRIES	Adm.	24	48	HOURS 72	96	120	144
HCT	44	42	40	34	34	34	34
CO_2	26	24	25	23	21	18	21
Na	133	131	138	135	140	140	140
Cl	99	90	95	95	95	99	100
K	5.4	4.9	6.5	5.4	6.0	5.7	5.3
NPN	36	38	36	33	30	35	32
T.Pro.	5.4	5.5	4.8	3.6	4.8	5.1	5.3
Alb.	3.2	3.1	2.6	2.1	2.7	2.7	3.2
Glob.	2.2	2.4	2.2	1.5	2.1	2.4	3.1
pH	7.46	7.45	7.45	7.45	7.42	7.42	7.42

CHART 1.

is required. When colloids are given, they should be given in a separate vein, if at all possible, so that electrolyte administration may be continuous. If no other vein is available without a cutdown, plasma may be given concomitantly with the electrolyte solution by introduction of the needle from the plasma bottle into the tubing containing the electrolyte solution.

The following case reports illustrate, in general, our method of early treatment of burns in infants and children with comments on the adequacy and inadequacy of treatment of individual cases reported:

CASE 1 (Chart 1). D. M. C., a 17.5 kilogram 6 year old male, sustained a 21.5 per cent burn (with estimated 18 per cent deep second and third degree burn).



HOURS

CHEMISTRIES	Adm.	24	48	72	96	120	144
HCT	41	33	32	34	33	33	31
CO_2	21	25	25	25	25	24	24
Na	132	140	142	140	139	140	140
Cl	100	100	100	96	100	100	100
K	4.7	5.1	4.2	4.4	4.5	4.5	4.4
NPN	39	31	32	31	31	31	30
T.Pro.	3.47	4.9	4.7	4.8	4.7	4.7	4.8
Alb.	2.04	2.9	2.8	2.8	2.8	2.8	2.8
Glob.	1.43	2.0	1.9	2	1.9	1.9	2.0
pH	7.45	7.47	7.47	7.45	7.45	7.44	7.44

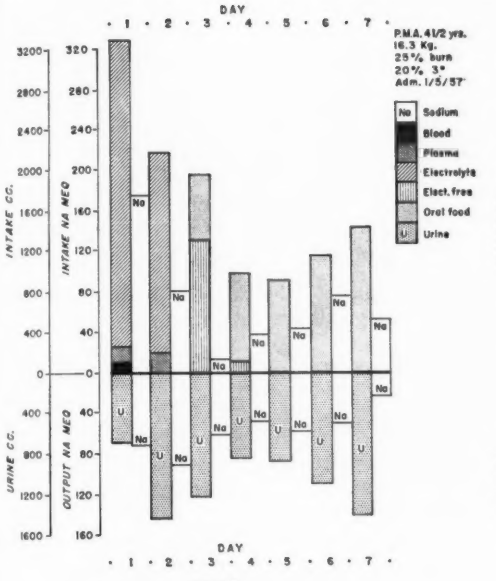
CHART 2.

Initial treatment consisted of 5 per cent glucose in Ringer's lactate. Adequate urinary output was obtained in 2 hours. This Ringer's lactate solution was discontinued after 4 hours. Six hundred cubic centimeters of this solution were given. Then a 4:6 solution was given (400 c.c. of 5 per cent glucose in Ringer's lactate and 600 c.c. of 5 per cent glucose in water) which was continued until the end of 24 hours postburn. Then a 3:7 solution was given (300 c.c. 5 per cent of glucose in Ringer's lactate and 700 c.c. of 5 per cent glucose in water) which was continued until the end of 48 hours. The patient was then started on oral fluids with supplemental intravenous 10 per cent invert sugar in water. He was given 300 cubic centimeters of stored plasma and 150 cubic centimeters of whole blood the first 24 hours and 150 cubic centimeters of plasma the second 24 hours. His blood pressure remained stable throughout. Sodium intake and output reached an equilibrium the third day.

CASE 2 (Chart 2). W. G. was a 13 month old male infant, weight 13.3 kilograms, who sustained a 25 per cent burn (with estimated 15 per cent third degree). He was given 200 cubic centimeters of 5 per cent glucose in Ringer's lactate the first hour following admission. Adequate urinary output was established. He was then given a 4:6 solution (400 c.c. of 5 per cent glucose in Ringer's lactate and 600 c.c. of 5 per cent glucose in water) which was continued until the end of 24 hours postburn. He was then given a 3:7 solution (300 c.c. of 5 per cent glucose in Ringer's lactate and 700 c.c. of 5 per cent glucose in water) until the end of 48 hours. He was then given intravenously 10 per cent invert sugar in water, and hourly oral feedings were started. One hundred and fifty cubic centimeters of plasma and 50 cubic centimeters of blood were administered the first 24 hours, and 100 cubic centimeters of plasma the second 24 hours. Because of low serum proteins he was given 75 cubic centimeters of plasma the third day. Sodium intake and output were stabilized the fourth day.

CASE 3 (Chart 3). P. M. A., a 4 year old male child, weight 16.3 kilograms, sustained a 25 per cent burn (20 per cent of it deep second and third degree). Initial treatment consisted of 350 cubic centimeters of 5 per cent glucose in Ringer's lactate over a 2 hour period with establishment of urinary output. Then a 4:6 solution was given (400 c.c. of 5 per cent glucose in Ringer's lactate and 600 c.c. of 5 per cent glucose in water). At the end of 24 hours he was given a 3:7 solution (300 c.c. of 5 per cent glucose in Ringer's lactate and 700 c.c. of 5 per cent glucose in water) which was continued until the end of 48 hours. The patient was then given 10 per cent invert sugar in water intravenously with frequent oral feedings. Colloid support consisted of 100 cubic centimeters of plasma started 4 hours after admission. A total of 160 cubic centimeters of plasma and 100 cubic centimeters of blood the first 24 hours and 180 cubic centimeters of plasma the second 24 hours was given. His blood pressure remained stable throughout. Sodium intake and output reached equilibrium the fifth day.

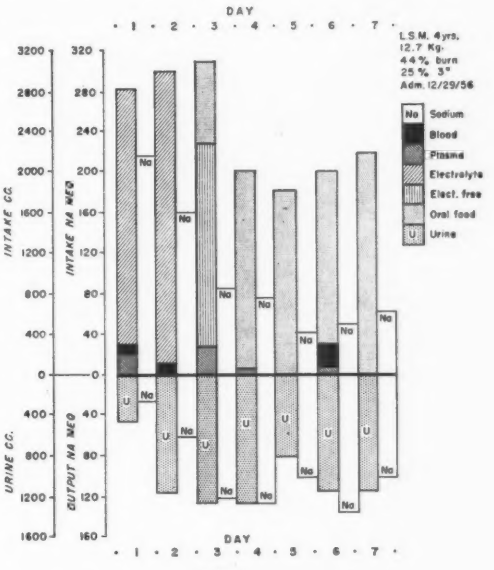
CASE 4 (Chart 4). L. S. M., a 4 year old female child, weighing 12.7 kilograms, suffered a 44 per cent burn (25 per cent third degree). She was given 5 per cent glucose in Ringer's lactate. It took 4 hours to establish an adequate urinary output. Six hundred cubic centimeters of this solution were given. She was then put on a 6:4 solution (600 c.c. of 5 per cent glucose in Ringer's lactate and 400 c.c. of 5 per cent glucose in water) until the end of 24 hours; then a 4:6 solution was given (400 c.c. of 5 per cent glucose in Ringer's lactate and 600 c.c. of 5 per cent glucose in water) until the end of 48 hours. Then she was put on 10 per cent invert sugar in water intravenously, and oral feedings were instituted. She received as colloid support 175 cubic centimeters of plasma and 75 cubic centimeters of blood in the first 24 hours, 100 cubic centimeters of blood in the second 24 hours, and 225 cubic centimeters of plasma the third 24 hours. Though she suffered no ill effects, it is believed that not enough colloid support was given the first 48 hours, necessitating additional support thereafter. Low serum proteins were noted the third day. Additional blood and plasma were given the sixth day because of a low hematocrit



HOURS

CHEMISTRIES	Adm.	24	48	72	96	120	144
HCT	41	42	38	34	32	32	32
CO_2	21	21	23	27	26	26	26
Na	140	139	140	138	138	139	140
Cl	100	100	100	95	97	98	100
K	6.1	5.7	4.8	5.4	4.7	4.8	4.7
NPN	36	35	27	31	31	30	31
T.Pro.	6.2	5.4	5.3	5.5	5.5	5.6	5.6
Alb.	3.5	2.9	2.9	2.9	2.9	3.0	3.0
Glob.	2.7	2.5	2.4	2.6	2.6	2.6	2.6
pH	7.35	7.42	7.45	7.45	7.45	7.45	7.45

CHART 3.



HOURS

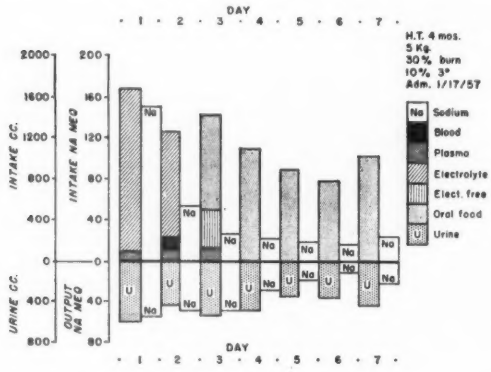
CHEMISTRIES	Adm.	24	48	72	96	120	144
HCT	50	54	50	49	33	29	30
CO_2	14	16	16	16	19	21	21
Na	154	140	140	151	146	130	140
Cl	107	102	103	104	103	100	100
K	7.5	5.8	6.3	5.3	5	4.5	4.2
NPN	29	50	50	24	39	42	26
T.Pro.	5.6	4.5	4.2	4.5	5.2	5.2	4.8
Alb.	4.2	2.9	2.7	2.9	3	3	3
Glob.	1.3	1.6	1.5	1.6	2.2	2.2	1.8
pH	7.3	7.4	7.45	7.45	7.45	7.45	7.45

CHART 4.

and continued low plasma proteins. Sodium intake and output were moderately well stabilized by the sixth day.

CASE 5 (Chart 5). H. T. was a 4 month old male infant, weighing 5 kilograms, who sustained a 30 per cent burn. An estimate of 10 per cent third degree burn was made originally. (Eighteen per cent was later recognized as deep second degree burn.) An adequate urinary output was not obtained for 8 hours. This was due to inadequate intravenous electrolyte administration necessitating 500 cubic centimeters of 5 per cent glucose in Ringer's lactate before establishment of adequate output. He was then put on a 6:4 solution (600 c.c. of 5 per cent glucose in Ringer's lactate and 400 c.c. of 5 per cent glucose in water) until the end of 24 hours; then a 4:6 solution was given (400 c.c. of 5 per cent glucose in Ringer's lactate and 600 c.c. of 5 per cent glucose in water) until the end of 48 hours. Then he was given 10 per cent invert sugar in water intravenously along with frequent oral feedings. Because it was not recognized that more deep second degree burn was involved, he received inadequate colloid support the first 24 hours. Because of low blood pressure readings of 90 to 98 systolic he was given plasma support. He was given 75 cubic centimeters of plasma the first 24 hours; then was given 75 cubic centimeters of plasma and 75 cubic centimeters of blood the second 24 hours, and 75 cubic centimeters of plasma the third day. On the third day his blood pressure reading was 280/60. This hypertension persisted for about 5 weeks. It is believed that the hypertension reflected early renal ischemia from lack of early vigorous electrolyte and colloid therapy. This opinion is probably substantiated by the mild acidosis and elevation of the nonprotein nitrogen at the fifth and sixth days. Sodium intake and output were stabilized by the fourth day.

CASE 6 (Chart 6). J. V., a 2½ year old male child, weighing 13 kilograms, sustained a 60 per cent second degree burn. The patient was initially given 5 per cent glucose in Ringer's lactate. Urinary output was established in 3 hours. Six hundred cubic centimeters of



CHEMISTRIES	Adm.	24	48	HOURS 72	96	120	144
HCT	38	32	33	32	35	38	38
CO_2	15	25	16	20	20	15	15
Na	141	140	140	151	145	140	138
Cl	102	100	101	102	102	100	100
K	6.4	5.2	4.5	6.1	6	6	6
NPN	59	39	45	42	56	56	64
T.Pro.	4.3	4.6	5.7	5.9	6.2	6.6	6.3
Alb.	3.6	3.4	3.4	3.7	3.7	4.4	3.6
Glob.	1.3	1.2	2.3	2.2	2.4	2.3	2.7
pH	7.42						

CHART 5.

this solution were given. He was then given a 6:4 solution (600 c.c. of 5 per cent glucose in Ringer's lactate and 400 c.c. of 5 per cent glucose in water) until the end of 24 hours; then he was given a 4:6 solution (400 c.c. of 5 per cent glucose in Ringer's lactate and 600 c.c. of 5 per cent glucose in water) until the end of 48 hours. He was then given intravenously 10 per cent invert sugar in water and frequent oral feedings were begun. One hundred cubic centimeters of plasma were given the first day and 75 cubic centimeters the second day. His blood pressure remained stable throughout the period of treatment. Sodium intake and output were stabilized by the sixth day.

No particular mention has been made of the blood chemistries, as they are self-evident with each of the cases. All blood chemistries were determined by microtechnique methods, and controls were run on each sample tested.

It has been observed that in spite of a low quantity of blood administered in the majority of cases, the hematocrit did not fall abnormally after the initial hemoconcentration period. The child's normal hematocrit is 35 volumes per cent. It was observed that when stored plasma support was not used, the total protein fell very low on the third and fourth days. In some cases, a rather high potassium level was observed at the second or third day. Clinically, this had no adverse effects. No case of hypokalemia was noted at the end of the study period. Formerly, the patients were given supplemental potassium starting at the fourth day, but recently this procedure has not been carried out provided that the patients are eating well, because most foods have a high potassium content.

The method of treatment has been altered in the following categories: Burns greater than 30 per cent, burns of between 15 and 30 per cent, and superficial burns of less than 15 per cent. The first 3 cases presented were of patients with burns of between 15 and 30 per cent. The second group of 3 cases consisted of burns of greater than 30 per cent. Blood pressure readings are extremely important and can be taken in the infant and child as well as the adult. Even in the severe burn of the upper extremity there is usually an area of normal tissue in one of the cubital fossae, and, by applying sterile gauze over the arm, the blood pressure cuff may be applied over it.

One may easily misestimate by the use of any formula the need for colloid support, and hypotensive blood pressure readings may be the first indication for additional support.

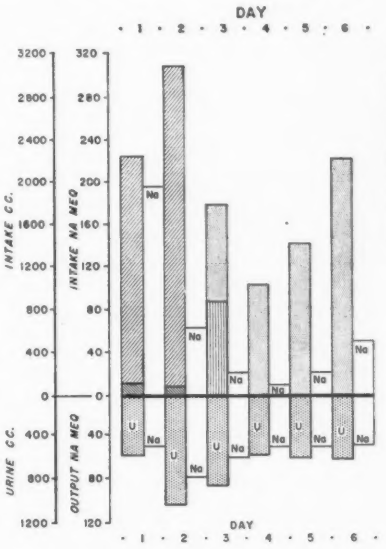
Once urinary output has been established, increasing quantities of fluid necessary to maintain a minimal urinary output constitute another indication for additional colloid support. Nothing is allowed by mouth during the first 48 hours in burns of greater than 15 per cent of the body surface, so that intake and output may be more meticulously regulated.

A number of adults with extensive burns have been treated by this method with successful results.

The following list of instructions outlines the present method of fluid and colloid treatment:

EARLY THERAPY IN THE TREATMENT OF BURNS

A. Burns of greater than 30 per cent:
   1. Electrolytes.
      a. Immediately do cutdown and start 5 per cent glucose in Ringer's lactate (the water and electrolyte losses are greatest during the first hour postburn). Allow nothing by mouth for 48 hours; 1,000 to 2,000 c.c. may be required in the first hour for the adult with a massive burn; 170 to 200 c.c. may be required for the infant. Continue to give solution until urinary output has been established (50 c.c. per hour in the adult, 25 c.c. per hour in a 5 year old child, 18 to 20 c.c. per hour in the infant).
      b. When urinary output has been established for a period of more than 1 or 2 hours: Mix a 6:4 solution of 600 c.c. of 5 per cent glucose in Ringer's lactate and 400 c.c. of 5 per cent glucose in water. Administer this solution until the end of 24 hours from time of burn. Rate of administration is to be governed by urinary output provided the patient is normotensive. Fluid orders for following hour should be in accordance with the urinary output of the previous hour. Try to keep urinary output within 15 c.c. of its optimum.
      c. From 24 to 48 hours: Mix a 4:6 solution of 400 c.c. 5 per cent glucose in Ringer's lactate and 600 c.c. 5 per cent glucose in water. Continue fluid administration as in (b).
      d. From 48 hours: Stop all I.V. sodium containing fluids. Start 10 per cent invert sugar in water I.V. Allow oral feedings each hour for 24 hours. Note: Rate of I.V. solution is governed by urinary output and amount of oral feeding intake. From this point on one does not have to be so strict with limitation of urinary output as water is being mobilized from wound edema. Avoid an excess of fluid administration during this 2 day period.
      e. From 60 hours: Semiliquid or soft diet. Increase amount of feeding each 12 hours if tolerated. Gradually increase time between feedings. Do not force feed the first week postburn.
   2. Colloid Therapy. Formula: Kgm. × per cent third degree burn or deep second degree burn × 1 = colloid c.c. in first 24 hours (limit estimate to a 50 per cent burn).
      a. Give one-half of this formula in the first 8 hours and one-half the second 24 hours. Note: All of the early colloid administration is in the form of stored plasma. Near the end of the first 24 hours a small quantity of blood is given.
      b. Administer plasma and blood in separate veins so that electrolyte administration can be continuous. Try to start plasma administration in the first 3 hours after admission to the hospital.
      c. The second 24 hours give one-half the amount of plasma and blood given the first 24 hours.



CHEMISTRIES	HOURS	Adm.	24	48	72	96	120	144
	HCT	51	46	35	34	36	36	35
	CO_2	20	20	19	22	28	28	26
	Na	143	148	132	137	138	138	140
	Cl	100	106	99	99	100	100	99
	K	6.1	7.6	6.6	5.2	6.0	6.0	5.9
	NPN	45	42	28	36	36	36	40
	T.Pro.	5.0	4.3	3.9	4.0	5.1	5.1	4.6
	Alb.	3.4	2.8	2.7	2.7	2.9	2.9	2.9
	Glob.	1.6	1.5	1.2	1.3	2.2	2.2	1.7
	pH		7.3	7.3	7.4	7.48	7.48	7.45

CHART 6.

      d. Check blood pressure each hour. Note: It is extremely important to keep the patient normotensive as the urinary output will not reflect underhydration or overhydration if the kidney filtration pressure (blood pressure) is inadequate. Hypotension may be reflected as a blood pressure of under 110 systolic in the adult and under 100 in the child or, if after initial urinary output has been established, it starts decreasing notwithstanding an increased I.V. intake. If such occurs, give more than your previous estimate. Ordinarily, colloids are not required in a second degree burn, but if it is extensive, plasma may be required. The need for colloid support may be evidenced by signs of hypotension mentioned in the previous paragraphs.

B. Burns of 15 to 30 per cent:
   1. Electrolytes.
      a. Allow nothing by mouth for 48 hours.
      b. Initially start 5 per cent glucose in Ringer's lactate until urinary output has been established as in (A).
      c. Then give a 4:6 solution of 400 c.c. of 5 per

cent glucose in Ringer's lactate and 600 c.c. of 5 per cent glucose in water. Administer this solution until the end of 24 hours from time of burn.

d. From 24 to 48 hours: Give a 3:7 solution of 300 c.c. of 5 per cent glucose in Ringer's lactate and 700 c.c. of 5 per cent glucose in water.

e. At the end of 48 hours give no sodium-containing fluids intravenously but follow regimen outlined in (A) after 48 hours post-burn.

2. Colloid Therapy. Observe regime outlined in (A).

C. Burns of under 15 per cent (superficial): Formula: Kgm. × per cent burn × 2 = c.c. Moyer's solution to be given by mouth in first 24 hours (no more — no less). Allow patient food and liquids ad lib.

SUMMARY

Physiologic principles of fluid and colloid losses have been reviewed. The importance of rapid replacement of these losses has been emphasized. Urinary output is a reliable guide for treatment, provided it is established early and the patient is kept normotensive.

The use of stored plasma as the principal colloid support has proved satisfactory and no case of homologous serum jaundice has been observed.

Case reports with illustrative fluid and sodium intake and output and accompanying blood chemistry determinations have been given, altering treatment in those incurring less than and those incurring greater than a 30 per cent burn. A summary sheet of our fluid and colloid treatment is included.

Our present concept of fluid and electrolyte replacement is that fluid with a concentrated electrolyte solution should be given rapidly *early* when the losses are greatest, and that later when the losses become more gradual, fluids which contain less concentrated electrolytes should be given more slowly.

It has been emphasized by Talbot that resorption of fluids and electrolytes is more rapid when repair solutions are used which are less concentrated, once the initial rapid losses have been controlled. To eliminate abnormal hormonal responses, fluids containing electrolytes are given continuously for the first 48 hours. After 48 hours, when resorption of sodium-containing fluids normally occurs, no intravenous sodium is administered.

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AEROBACTER AEROGENES BACTEREMIA AND BACILLURIA

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In 1949, Wilhelm and Orkin reported a striking increase in the frequency of Aerobacter aerogenes among urinary tract infections. In an analysis of two series of consecutive cases, it was revealed that the incidence had risen from 7.3 per cent in the 1940 to 1941 period to 49.2 per cent in the period between 1945 and 1948. They reported 4 cases of bacteremia by Aerobacter aerogenes with 1 recovery. Eighty-eight per cent were resistant to 16 units of streptomycin. Thirty-two patients were treated with streptomycin; 7 cases cleared up and 21 persisted. In 73 per cent of 93 patients, the infection persisted. They concluded that Aerobacter aerogenes is often resistant to the commonly used therapeutic agents.

Waisbern, in 1951, reported 7 cases (22.5 per cent) of Aerobacter aerogenes bacteremia among 31 cases of gram-negative rod bacteremia with a mortality rate of 25 per cent. Six of these 7 cases followed genitourinary tract infections.

Koch, in 1956, reported 56 cases of bacteremia due to gram-negative rods, of which 13 (26 per cent) were Aerobacter aerogenes bacteremia with a mortality rate of 23 per cent. Six of these cases followed surgery, and 4 followed catheterization.

Martin and associates, in 1954, reported 20 cases of Aerobacter aerogenes bacteremia during the 1940 to 1953 period, with 15 per cent mortality. Twelve patients had surgical intervention, and 15 cases were secondary to genitourinary tract infections. Keefer and Hewitt consider portals of entry to be urinary tract, postoperative wounds, and biliary tract, with a mortality rate of 26 per cent.

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In 1949, Carroll reported an incidence at the St. Louis Hospital, in 1947, of 7.5 per cent Aerobacter aerogenes among the inpatients and 5 per cent among the private patients. In addition to the 7.5 per cent incidence of Aerobacter aerogenes, there were incidences of Escherichia coli (26.6 per cent), Pseudomonas aeruginosa (10 per cent), micrococcus (8 per cent), Streptococcus—all types (8 per cent), and Proteus vulgaris (4 per cent). A recent study (1957) on this urologic service showed that in acute or recent infections, the incidence of gram-negative rod infections was 50 per cent; Enterococcus incidence was 21.1 per cent; Bacillus proteus 16.6 per cent; Aerobacter aerogenes 14.2 per cent; Escherichia coli 12.6 per cent; Micrococcus pyogenes aureus 12.6 per cent; Pseudomonas aeruginosa 8 per cent; Gaffkya tetragena 5.5 per cent; diphtheroids 6.3 per cent; Streptococcus nonhemolyticus 2.3 per cent; Streptococcus viridans 1.5 per cent; and paracolon 1.5 per cent. In chronic infections, in which there have been repeated hospital admissions, out-patient visits, or repeated use of chemotherapy, the incidence of gram-negative rod infections of the genitourinary tract was 80.5 per cent. The incidence of Aerobacter aerogenes was 39.0 per cent; Escherichia coli 13.7 per cent; Micrococcus pyogenes aureus 11.5 per cent; Bacillus proteus 16.3 per cent; Pseudomonas aeruginosa 9.7 per cent; Enterococcus 7.2 per cent; Gaffkya tetragena 1.4 per cent; Alcaligenes faecalis 0.3 per cent; and Klebsiella pneumoniae 0.7 per cent. It is thus evident that repeated chemotherapy or contact with medical centers causes an increase in the incidence of gram-negative rod infections of the urinary tract, especially with Aerobacter aerogenes.

AEROBACTER

Aerobacter aerogenes are short, gram-negative, usually nonmotile rods which grow readily on ordinary media, fermenting glucose, lactose, fructose, galactose, arabinose, maltose, raffinose, cellobiose, salicin, esculin, starch, dextrin, glycerol, mannitol, sorbitol, and inositol with the production of acid and gas. Carbon dioxide production from glucose is double or more that of hydrogen. The methyl-red test is negative while the acetylmethyl carbinol (Voges-Proskauer) test is positive. Trimethylene glycol is not produced from glycol by anaerobic fermentation. Citric acid and salts of citric acid are utilized as the sole sources of carbon, and uric acid may be utilized as the sole source of nitrogen; sodium hippurate is hydrolyzed, nitrites are produced from nitrates, indole may or may not be produced, hydrogen sulfide is not produced, gelatin is rarely liquefied, and acid gas is produced from glycol. Normally it is found on grains and plants, in water, milk, dairy products, and intestinal canals of man and animals, and is widely distributed in nature.

Aerobacter cloacae differs from Aerobacter aerogenes in a few minor features. It is usually motile, does not hydrolize sodium hippurate, and does not produce indole. Glycerol is fermented with the production of no visible gas, and gelatin is liquefied.

Escherichia coli are short, gram-negative, motile, or nonmotile rods producing acid and gas in glucose, fructose, galactose, maltose, arabinose, xylose, rhamnose, and mannitol. Sucrose, raffinose, salicin, esculin, dulcitol, and glycerol may or may not be fermented. Inulin, pectin, and adonitol are rarely fermented, and dextrin, starch, glycogen, inositol, cellobiose, and methyl glycoside are not fermented. Approximately equal volumes of carbon dioxide and hydrogen are produced from glucose. Trimethylene glycol is not produced from glycerol by anaerobic fermentation. Citric acid and citric acid salts are not utilized as sole sources of carbon, and uric acid is not utilized as a sole source of nitrogen. Indole is usually produced, but hydrogen sulfide is not. The methyl-red test is positive, but the acetylmethyl carbinol test (Voges-Proskauer) is negative.

To date, approximately 135 O groups, 75 antigens, and 40 H antigens have been recognized and characterized in Escherichia. These antigens may occur in different combinations, and therefore, the number of serotypes existing within the species is much greater than recognized to date.

Within recent years, there has been a great increase of interest in the serology of Escherichia coli due to the association of certain serotypes with severe outbreaks of infantile diarrheas, i.e., 026:B6; 055:B5; 0111:B4; 0127:B8; and 0128:B12.

Escherichia coli is a normal inhabitant of the intestinal tract of man and vertebrates, is distributed widely in nature, and frequently causes infections of the genitourinary tract and diarrhea in infants. It may invade the circulation in agonal stages of diseases. Four varieties are recognized, i.e., Escherichia coli var. communis, Escherichia coli var. acidi-lactici, Escherichia coli neapolitana, and Escherichia coli var. communior. The other recognized species of this genus are Escherichia aurescens, Escherichia freundii, and Escherichia intermedia.

PATHOGENESIS

According to Rattner and Murphy (1957) the mechanism of bacterial shock in bacteremia of genitourinary tract infections is due to: (1) direct action of bacteria or toxins upon the capillary walls; (2) effect of histamine-like substances or proteins, degradation products of bacterial enzyme activity, upon the vascular tree; (3) effect of bacterial toxins on the medullary vasomotor centers or regional sympathetic ganglia; (4) action of the toxins on the heart; (5) hemolysis, alteration of hemoglobin by bacteria or bacterial products contributing to hypoxia; (6) adrenal insufficiency produced by an unknown mechanism.

We cannot completely agree with this concept because, in our experience, the

gram-negative rods fail to produce exotoxins, except for Shigella shigae, which does not invade the systemic circulation and cause bacteremia. It is possible, however, that bacterial endotoxins and enzymatic end-products give rise to the symptomatology of toxemia associated with bacteremia.

Escherichia and Aerobacter are non-pathogenic as long as they remain in the gastrointestinal tract, but occasionally the former has been blamed for the causation of infantile diarrhea. Anytime they gain access to tissues outside the intestinal tract, they become pathogenic and give rise to genito-urinary tract infections, abscesses, bacteremia, peritonitis, biliary tract infections, and even pneumonitis and central nervous system and skeletal system infections.

Prior to the extensive use of antibiotics, the biologic differences between these two genera were not reflected in the clinical manifestations. In the presumptive test for Escherichia coli for the laboratory testing of water, it was considered that the presence of Escherichia coli indicated fecal contamination of the water, and therefore, such water could contain other bacteria of fecal origin, such as Salmonella or Shigella. On the other hand, if Aerobacter was found, the water was safe for human consumption. As a matter of fact, most laboratories, even at present, do not distinguish between Escherichia and Aerobacter. They either report Escherichia coli or coliform bacteria. It is absolutely essential that coliform bacteria be definitely classified and identified because: (1) There is a difference in the pathogenesis of Escherichia and Aerobacter. (2) Aerobacter can undergo mutation while Escherichia does not. (3) Aerobacter infections may be more severe and give a poorer prognosis.

Weil and Stempel (1955) reported that more than one-third of the coliform bacteria isolated during the 1953 to 1954 period were resistant to tetracycline. During the same period, Kirby and associates (4) reported that 29 per cent of coliform bacteria was resistant to tetracycline, and 43 per cent was resistant to streptomycin. Resistant coliform bacteria probably evolved in patients with chronic infections as a result of repeated therapy with drugs, who had acquired these infections in hospitals and probably had had instrumentation of the urinary tract. About 20 to 40 per cent of coliform bacteria isolated at various intervals were antibiotic resistant. These resistant strains were recovered from patients who had chronic infections, had varied chemotherapy, had been in hospitals or clinics, and usually were associated with instrumentation. Kirby and Corporn (3) (1956) recovered coliform bacteria from 85 patients, 44 of which were antibiotic resistant and half of which were sensitive to polymyxin, while the remaining were sensitive to both polymyxin and chloramphenicol. Antibiotic sensitive strains were encountered usually among acute infections at the time of hospital admission. The incidence of obstructive lesions of the urinary tract was low and there were few instances of instrumentation. Ten of the 41 patients with antibiotic-sensitive organisms had bacteremia. There was a definite correlation between antibiotic resistant strains and instrumentation, and many of these patients entered the hospital without symptoms of the urinary tract, the urine becoming infected only after a catheter had been placed for many days or after urinary tract obstruction.

PRESENT STUDIES

During the 5 year period from 1952 to 1957, at the Columbia-Presbyterian Medical Center, there were 74 cases of bacteremia with gram-negative rods. Table I shows the incidence of various microorganisms in such bacteremias. The mortality rate was 37.8 per cent.

There were 29 cases of Escherichia coli bacteremia (5 of which were among children) with 11 deaths (5 male adults and 6 female adults). There were 10 cases of Aerobacter aerogenes bacteremia, with 6 deaths, 1 of which was of the only child in this series. There were 12 instances of Salmonella bacteremia, with 1 death, that of the only adult in that group. Of the 12, there were: 2 in-

TABLE I.—GRAM-NEGATIVE ROD BACTEREMIA AMONG 74 PATIENTS DURING THE 5 YEAR PERIOD, 1952 TO 1957

	Dead		Alive		Total		
	Children	Adults	Children	Adults	Children	Adults	Both
Escherichia coli	—	11	5	13	5	24	29
Aerobacter aerogenes	1	5	—	4	1	9	10
Salmonella sp.	—	1	11	—	11	1	12
Bacillus proteus	1	3	—	3	1	6	7
Alcaligenes faecalis	1	—	—	1	1	1	2
Pseudomonas aeruginosa	2	1	—	1	2	2	4
Hemophilus influenzae	—	—	7	—	7	—	7
Klebsiella pneumoniae	—	—	—	1	—	1	1
Pseudomonas aeruginosa and Escherichia coli	1	—	—	—	1	—	1
Gram-negative rod	1	—	—	—	1	—	1

Mortality rate, 28 of 74 (37.8 per cent).

TABLE II.—THE BACTERIAL FLORA IN CHRONIC AND ACUTE INFECTIONS OF THE URINARY TRACT

	Chronic or recurring infections			Acute infections or new cases	
	No. of cultures	Per cent of incidence		No. of cultures	Per cent of incidence
Aerobacter aerogenes	277				
	108	39.0		30	14.2
Escherichia coli	38	13.7		16	12.6
Micrococcus pyogenes aureus	32	11.5		16	12.6
Bacillus proteus	45	16.3		21	16.6
Pseudomonas aeruginosa	27	9.7		6	8.0
Enterococcus	20	7.2		27	21.1
Gaffkya tetragena	4	1.4		7	5.5
Klebsiella pneumoniae	2	2	0.7	—	—
Diphtheroids	—	—		8	6.3
Streptococcus viridans	—	—		2	1.5
Streptococcus non-hemolyticus	—	—		3	2.3
Paracolon	—	—		2	1.5
Alcaligenes faecalis	1	0.4	.03	—	—

stances of Salmonella choleraesuis (1 death); 2 of Salmonella schottmülleri; 2 of Salmonella group Cl; 3 of Salmonella oranienberg; 2 of Salmonella st. paul; and 1 of Salmonella typhimurium.

In addition, there were 2 cases of Alcaligenes faecalis with 1 death (a child); 7 cases of Bacillus proteus with 4 deaths, 1 of which was of the only child in this group; 4 cases of Pseudomonas aeruginosa with 3 deaths, 2 of which were of children; 7 children with Hemophilus influenzae type B with no deaths; 1 case of Klebsiella pneumoniae with recovery; 1 case of Pseudomonas aeruginosa and Escherichia coli with death; and 1 case of unidentified gram-negative rod with death. Twenty-eight deaths among 74 patients with gram-negative rod infections, a mortality rate of 37.8 per cent.

AEROBACTER AEROGENES BACILLURIA

From one series of 60 patients suffering from acute urinary tract infections, 126 urine cultures were obtained. Thirty grew out Aerobacter aerogenes, 16 Escherichia coli, 16 Micrococcus pyogenes aureus, 21 Bacillus proteus, 6 Pseudomonas aeruginosa, 27 Enterococcus, 7 Gaffkya tetragena, 8 diphtheroids, Streptoccus viridans, 3 nonhemolytic streptococcus, and 2 paracolon. Enterococcus is the commonest causative agent in acute urinary tract infections.

Moreover, 277 cultures were obtained from 236 patients suffering with chronic urinary tract infections. One hundred and eight grew Aerobacter aerogenes, 38 Escherichia coli, 45 Bacillus proteus, 27 Pseudomonas aeruginosa, 32 Micrococcus pyogenes aureus, 20 Enterococcus, 4 Gaffkya tetragena, 2 Klebsiella pneumoniae, and 1 Alcaligenes faecalis. It is, thus, obvious that Aerobacter aerogenes has now become a very common infecting organism for the urinary tract.

DRUG SUSCEPTIBILITY STUDIES

The tube dilution method for determining susceptibility was performed on all 108 Aerobacter aerogenes cultures obtained from the 236 patients suffering from chronic infections.

Table III shows that 97 of the 108 were very resistant to furadantin, 9 resistant, 1 sensitive, and 1 very sensitive. Sixty-nine of

91 were very resistant to sulfadiazine, 12 resistant, 2 sensitive, and 8 very sensitive. Fifty-five of 65 were very resistant to gantrisin, 4 resistant, 2 sensitive, and 4 very sensitive. Ten of 10 were very resistant to thiosulfil. Ninety-three of 108 were very resistant to tetracycline, 7 resistant, 3 sensitive, and 5 very sensitive. Sixty-six of 108 were very resistant to chloramphenicol, 16 resistant, 17 sensitive, and 9 very sensitive. Ninety-nine of 103 were very resistant to erythromycin, 3 resistant, and 1 very sensitive. Fifty-six of 67 were very resistant to novobiocin, and 11 were resistant. Eighty-four of 100 were very resistant to penicillin + streptomycin, 8 resistant, 6 sensitive, and 2 very sensitive. Ninety-five of 104 were very resistant to streptomycin, 2 resistant, 4 sensitive, and 3 very sensitive. Eighteen of 20 were very resistant to matromycin and 2 very sensitive.

Clinically speaking, there is nothing characteristic of Aerobacter aerogenes infections. The symptoms and the signs are no different from those due to infections caused by other organisms. The characteristic feature is that this organism is very stubborn to chemotherapy and has a very great tendency to persist despite all therapeutic agents.

Another feature is that infections can be acquired readily in hospitals or clinics, regardless of the strictness of antibacterial precautions. There is the possibility that invasion may take place from the intestinal tract by any member of the coliform group, but Escherichia coli, being readily controlled by chemotherapeutic agents, is eliminated easily, while Aerobacter aerogenes, being resistant, may attain a strong foothold in any part of the urinary tract. A second factor is the nature of Aerobacter aerogenes to mutate to a resistant form while Escherichia coli does not. Experimental studies indicate that Aerobacter aerogenes can acquire resistance to 3.5 milligrams of tetracycline, while Escherichia coli does not.

In the presence of Aerobacter aerogenes infection of the urinary tract, it is advisable to postpone surgery of the urinary tract until the urine is sterile. Otherwise, there is always the risk of inducing Aerobacter aerogenes bacteremia with disastrous complications.

TABLE III.—FIELD SOLUTION SENSITIVITY TEST ON 108 AEROBACTER AEROGENES CULTURES OBTAINED FROM CHRONIC URINARY TRACT INFECTIONS

Drugs	*Very resistant*	*Resistant*	*Sensitive*	*Very sensitive*
Furadantin	97/108	9/108	1/108	1/108
Sulfadiazine	69/91	12/91	2/91	8/91
Gantrisin	55/65	4/65	2/65	4/65
Thiosulfil	10/10	0/10	0/10	0/10
Tetracycline	93/108	7/108	3/108	5/108
Chloramphenicol	66/108	16/108	17/108	9/108
Erythromycin	99/103	3/103	0/103	1/103
Novobiocin	56/67	11/67	0/67	0/67
Penicillin + streptomycin	84/100	8/100	6/100	2/100
Streptomycin	95/104	2/104	4/104	3/104
Matromycin	18/20	0/20	0/20	2/20

Very resistant organisms required more than 12.5 micrograms or units per milliliter antibiotic or furadantin, and more than 5 milligrams per milliliter sulfonamide.
Resistant organisms required 3.125 to 6.25 milligrams or units per milliliter antibiotic or furadantin, and 1.25 to 2.5 milligrams per milliliter sulfonamide.
Sensitive organisms required 0.78 to 1.56 milligrams or units per milliliter antibiotic or furadantin, and 0.31 to 0.62 milligram per milliliter sulfonamide.
Very sensitive organisms required less than 0.78 microgram or unit per milliliter antibiotic or furadantin, and less than 0.31 milligram per milliliter sulfonamide.

While awaiting the results of susceptibility tests, probably the best drug to use in treating Aerobacter aerogenes bacilluria is chloramphenicol or sulfadiazine. The second choice is penicillin plus streptomycin or tetracycline, and the third choice is gantrisin. An occasional organism may be found sensitive to furadantin, erythromycin, or matromycin.

AEROBACTER AEROGENES BACTEREMIA

Of 10 cases of Aerobacter aerogenes bacteremia, there was 1 in a child of 6 years who died of that infection. Six of the 10 cases were clear-cut instances of bacteremia following surgical intervention in the genitourinary tract. Four of these patients survived, but despite vigorous antibacterial and symptomatic treatment, the other 6 succumbed to Aerobacter aerogenes bacteremia. There is only 1 purely medical case in which Aerobacter aerogenes bacteremia

was a terminal phenomenon in disseminated lupus erythematosus. A second patient, both medical and surgical with hemochromatosis and diabetes, had a perforated gastric ulcer for which he had an abdominal operation. The third patient was a pediatric case in which the diagnosis was congenital atresia of hepatic bile ducts, biliary cirrhosis, and congenital double pelvis and double ureters with hypoplasia of the left kidney, left hydronephrosis, and ectopic ureteral orific in trigone and urethra, and can be considered a genitourinary case. Thus, of 10 patients, there was 1 medical case with terminal bacteremia, and 9 urologic or surgical cases in which Aerobacter gained access to the blood stream through surgery of the urinary tract.

In 4 patients who recovered from Aerobacter aerogenes bacteremia, the disease developed prior to 1954, but in 6 who died and 1 who recovered it developed in the period between 1954 and 1957. There was 1 death in 1954, 1 in 1955, 1 in 1956, and 3 in 1957. If this is the rate at which Aerobacter aerogenes is gaining speed in virulence or resistance to therapy, it should be watched very carefully.

CLINICAL COURSE

The clinical picture of Aerobacter aerogenes bacteremia may be sudden in onset, or insidious, from a previous medical or surgical condition. The onset is usually accompanied by a chill, fever, and perspiration (as a matter of fact, 1 patient, a Puerto Rican, was believed to have had malaria, and smears were examined for plasmodia). There is severe prostration, malaise, headache, vomiting, usually leucocytosis (7 of 10 patients had leucocytosis) with increase in neutrophils, elevation of erythrocyte sedimentation rate, drop in hemoglobin and red cell count and hematrocrit. The urine usually contains albumin, white and red blood cells, and microorganisms prior to bacteremia, which may or may not be Aerobacter. For example, 4 of 10 patients did not have Aerobacter in the urine, although all 10 grew Aerobacter aerogenes from the blood culture. Sooner or later, the blood electrolyte balance is disturbed with a drop of sodium and chlorides as well as bicarbonate of plasma. There is a gradual elevation of blood urea nitrogen. The blood pressure is lowered, and the pulse rate is increased. Urinary dysfunction is the most important finding. There is either progressive oliguria, or there is acute renal shutdown, with terminal uremia, coma, collapse, and death. With chemotherapy, recovery is either by crisis when the temperature drops down to normal within 24 hours, or comes down by lysis in about 3 days, or the bacteremia persists for about 2 weeks running a septic course, and coming down by lysis. On the other hand, in case the infection is overwhelming, or the organism is highly virulent, or resistant to chemotherapy or the resistance of the host is very poor, then, after 1 to 2 weeks of septic course the patient eventually collapses with renal shutdown and uremia.

Aerobacter aerogenes invasion of the circulatory system may be within the second to fourth postoperative day, 2 to 12 weeks, and in 1 case bacteremia developed a year after surgery. Immediate postoperative bacteremia gives a very bad prognosis. As a matter of fact, the 4 patients who recovered had bacteremia 2 days, and 2, 3, and 12 weeks following the genitourinary surgery, respectively. In the remaining 3 genitourinary patients who died, bacteremia developed 2 to 4 days postoperatively in 2 cases, and about a year later in the third.

MANAGEMENT

Four patients had Aerobacter aerogenes organism in the urine prior to bacteremia. Drug susceptibility tests are vital and are most informative when dilution method is used, and the minimum inhibitory concentrations of the drug are determined. Many of these patients have had only the disc susceptibility method employed. Two organisms were *sensitive* to streptomycin, 1 to terramycin, 1 to tetracycline, 1 to furadantin, 1 to chloramphenicol, 4 to neomycin,

and 4 to polymyxin. Two were *resistant* to penicillin, 4 to streptomycin, 1 to aureomycin, 4 to erythromycin, 1 to polymyxin, 1 to bacitracin, and 4 to chloramphenicol. In 3 patients, the organisms were not tested for sensitivity, and 2 of these patients recovered.

There is no clinical or therapeutic pattern followed in these patients. Antibiotics were used only on clinical grounds despite the fact that sensitivity tests were performed on 7 patients. Penicillin, streptomycin, tetracycline drugs, chloramphenicol, gantrisin, sulfadiazine, and furadantin were used. In 1 case, polymyxin was used parenterally for 1 day, and in another patient, neobacin was similarly used for 1 day by mouth. In 4 patients who recovered, oxytetracycline, streptomycin, chloramphenicol, penicillin, gantrisin, or furadantin were used either alone or in various combinations. On the other hand, the patients who succumbed to Aerobacter aerogenes septicemia received larger doses, and for longer periods of time, of several antibiotics and antibacterials.

These facts indicate that the medical profession is almost helpless in the chemotherapy of Aerobacter aerogenes septicemia. The prevention of infection is the desideratum, and this can be best accomplished through proper surgical and urinary planning.

SUMMARY

Because of marked differences in resistance to treatment employing chemotherapeutic agents, it has become imperative to differentiate infecting coliform organisms into Escherichia coli and Aerobacter aerogenes groups early in treatment.

Among 108 cases of Aerobacter aerogenes bacilluria, drug susceptibility studies indicated that Aerobacter aerogenes is a highly resistant organism, and that infections with this organism are very resistant to chemotherapy. Nevertheless, the drug of choice is most often chloramphenicol or sulfadiazine; second choice is penicillin plus streptomycin or tetracycline; as third choice, gantrisin is employed. An occasional organism may be sensitive to furadantin, erythromycin, or matromycin.

During the 5 year period from 1952 to 1957, 10 cases of Aerobacter aerogenes bacteremia occurred among 74 cases of gram-negative rod bacteremias at the Columbia-Presbyterian Medical Center. Four patients with aerogenes bacteremia recovered; 6 deaths occurred during the period between 1954 and 1957. Eight of 9 patients had had surgical intervention prior to bacteremia. In 1 case, it was a terminal medical complication. No universally effective chemotherapeutic program was observed. The final clinical picture was one of renal failure.

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EDITORIALS

SHOCK AND BLOOD PRESSURE

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AN ABNORMALLY LOW systolic blood pressure is characteristic of the clinical condition conveniently called shock. It is natural then, that the physician sometimes becomes obsessed with the compulsion to correct the abnormal blood pressure at all cost. At the turn of the century, great hopes were held for the newly prepared extracts of the adrenal medulla which had strong effects upon the blood pressure of experimental animals. Thus, clinicians had hoped that epinephrine would prove to be a great boon to mankind, because by means of it the correction of hypotension would be a simple matter. These hopes for solution of the problem of shock unfortunately were not supported by subsequent clinical and experimental observations. More recently, sympathomimetic agents with pharmacologic properties different from those of epinephrine have been prepared, and much has been written about their usefulness in clinical shock. Thus, it is wise to reconsider some basic principles upon which rests the rationale for the use of these agents in hypotension.

First, we must appreciate that the condition, which as clinicians we describe as shock, has many etiologic factors related only in that they have the same physiologic results, namely hypotension and poor perfusion of at least some tissues and organs. In some conditions, in which there is inhibition, depression, or block of vasoconstrictor activity, as in the case of extensive sympathectomy, high spinal anesthesia, or severe infections, one can find adequate justification for restoring the peripheral vascular resistance to normal by the use of vasoconstrictors. Even here, however, we must appreciate that the vasodilatation is not generalized. The fact that in high spinal anesthesia the increased blood flow in the skin of the extremities is not accompanied by an increase in cardiac output means that the blood flow in certain other vascular beds must be decreased. It is conceivable that the diminished blood flow in these sacrificial areas would be further exaggerated by the use of agents which were administered for the purpose of constricting the dilated vessels. Such vital organs as the kidney and the liver might thus suffer from ischemia. In spite of this, there are situations in which the hypotension is referable to decreased total perpheral resistance, and in these cases the use of vasoconstrictors may be reasonable in an effort to restore peripheral hemodynamics to normal.

Another principle to bear in mind is that the circulation conducts its affairs at the capillary. It is at the capillary level that solutes, gases, crystalloids, and colloids shuttle from one side to the other of the endothelial membrane which separates the blood from the tissue fluids. The blood pressure is only a means to this end. Little, if anything, is achieved for a tissue or organ by restoring the blood pressure in the large arteries if this is done at the expense of the

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capillaries by constricting the arterioles which control their blood supply. The action of the agent merely adds to the deprivation of those capillaries and the adjacent tissues. Cannon wrote in 1923, ". . . merely a higher arterial pressure is not the desideratum in the treatment of shock, but a higher pressure which provides an increased nutritive flow *through the capillaries all over the body*." To achieve this objective in wound shock, the prime consideration is restoration of the blood volume.

It is true that different vascular beds throughout the body react differently to nervous and humoral stimuli. L-norepinephrine causes a vigorous vasoconstriction in the skin, but an extraordinary vasodilatation in the myocardial blood vessels. The mechanism for this myocardial vasodilatation is not entirely clear, but this detail is not of prime importance for this discussion. There is some experimental evidence that renal hemodynamics approach normal when hemorrhagic hypotension is corrected (but not if overcorrected) by means of l-norepinephrine. Further study of this observation is needed. In skeletal muscle l-norepinephrine increases the rate of blood flow previously depressed by hemorrhage. The circulation of the brain of the dog is improved by l-norepinephrine when used during severe hypotension, but not when the systemic blood pressure is normal or only slightly depressed. The effects upon the circulation of the liver are not clear. On the basis of these observations, one would expect that the use of these agents would be beneficial in hypotension regardless of other considerations. This expectation has not been realized in our own clinical experience.

In the experimental animal, the data generally support the opinion expressed by Cannon 36 years ago. In the laboratory, when l-norepinephrine is used from the very start to maintain the blood pressure in the face of hemorrhage, the results in terms of mortality are better than when the hypotension is not corrected by this means. However, when this hypotension is permitted to last much longer than 5 minutes before l-norepinephrine is administered, the mortality is not improved; in fact, the treatment may reduce the chances of survival. In man, there are reports which claim beneficial effects from the use of pressor agents which restore the blood pressure primarily by increasing the peripheral vascular resistance. There probably are differences between the physiology of hypotension in man and that in the dog. Nevertheless, when one examines the available information on the reported patients who survived or died following the use of sympathicomimetic agents in hypotensive states, one comes to the conclusion that those patients who had serious abnormalities underlying the hypotension died, while those with relatively simple or trivial pathologic states lived. In these two groups of patients the mortalities and survivals are those which one would expect following surgical therapy without the use of pressor agents.

During the year 1958, 609 vials of metaraminol and 701 vials of l-norepinephrine were used in the Cleveland Metropolitan General Hospital for various situations, including oligemic shock. There has been no patient on the surgical services in whom survival could clearly be attributed to the restoration of blood pressure to normal or nearly normal levels by the use of these agents. We have seen no instance in which the sympathicomimetic amines alone restored the urinary output in hypotension with oliguria or anuria. It is entirely possible that the pressor agents were used in amounts that were too great or too small. We have explored many of the variables in this problem at the clinical level and the results have been the same.

In both medicine and surgery the physician must do everything possible for the critically ill patient even if resort must occasionally be made to empiricism. Risks often must be taken. However, the physician must not do harm either by commission or omission. When he plans to use the sympathicomimetic amines for hypotension, he

must remember that certain of the drugs do produce untoward effects. Serious cardiac arrhythmias after the use of l-norepinephrine have been reported both in animals and in man. More important is the matter of omission. At least in the preoperative and postoperative surgical wards, in operating rooms, and in emergency rooms, the most common cause of hypotension is oligemia of one kind or another. It is essential to direct one's efforts toward assessing the nature of the oligemia and toward correcting it as well as remedying its underlying cause. Sympathicomimetic agents should be reserved for situations in which it is clear that the hypotension is entirely or in large part due to vasomotor paralysis.

There are patients in whom it is impossible to maintain a normotensive state even when large volumes of appropriate fluids are infused. Here it may be "inconceivable" that oligemia exists. Nevertheless, in such cases, the physician must not rest in the semantic protective custody of "irreversible shock." He must be certain that oligemia in fact does not exist. The large volumes of infused blood could be flowing out into the pleural spaces, into the abdomen, or about a compound fracture. He must be certain that he is not dealing with relatively uncommon but fatal conditions such as tension pneumothorax, cardiac tamponade, or unrecognized but fatal infection.

Finally, there are situations in which hypotension has existed for so long, and the cells of certain tissues and organs have sustained such a deficiency in blood supply that they are about to die or have actually died. Death of tissues is a matter of definition. There are cells which live longer than the organism as a whole (by our clinical definition of death); and there are cells which die long before the animal dies. Different species, different individuals within the same species, and tissues within the same individual differ as to which cells die first as the result of inadequate perfusion during hypotension. The nature of the metabolic derangements which lead to cellular death remains to be clarified. It is understood, however, that once these intracellular metabolic derangements have progressed to a certain point the cells die and when enough vital cells have reached this stage, the animal itself dies.

Can these metabolic changes be reversed? It is in this area that more research is needed. The evidence at best is fragmentary, but it does appear that mere restoration of normal or supranormal perfusion, as in the case of the heart, may not reverse the abnormal metabolic processes when these have advanced too far. Possibly, the use of certain drugs may help metabolic recovery of cells that are hanging in the balance between death and survival. Such substances as autonomic blocking agents, cortisone and its derivatives, and certain antibiotics may contribute a shade of benefit. In these dire circumstances there may be a place for the temporary use of vasopressors along with large doses of substances such as hydrocortisone with or without antibiotics. However, it must be emphasized that this position is defensible only when the physician is quite certain that the circulating blood volume is not deficient, and that other readily correctable causes of hypotension have been thoroughly excluded. The empiric use of potent sympathicomimetic agents to raise the blood pressure can jeopardize the patient's chances for recovery. Not only do these substances sometimes have fatal untoward effects, but by permitting the physician to rest in the security of a normal arterial blood pressure, obtained at the expense of the capillary circulation beyond, they can contribute to a fatal outcome.

CANCER AND CACOTELIC OPERATIONS

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CACOTELIC: (kakos, Gr., a combining form meaning bad; and telikos, Gr., tending toward an end) meaning literally "tending to end badly."[1]

THE EFFORT and expense involved in the surgical treatment of cancer is sometimes not justified on the basis of the results. What has been undertaken in the hope of bringing relief from pain and suffering, or sometimes in the hope of cure, may bring only disappointment. Sometimes this is because the surgeon goes too far or does too much, or because of poor technique or selection one complication follows another, or because the tumor grows and spreads in spite of treatment or perhaps because of it. Whatever the reason, when it appears that if only the present complication can be surmounted all will be well, the surgeon must do everything he can to reverse the patient's downhill course. But again, his efforts are often futile. This is traumatic for all concerned. Such experiences leave deep scars on the mind of the surgeon as well as upon his patients, living and dead.

Why these predicaments? There are probably many reasons. Sometimes the surgeon proceeded because he believed that "something had to be done" or because he had an abundant faith in his ability and in the "benefits" of surgery. At other times he failed to recognize that the futility of surgical treatment was indicated by the extent and nature of the disease. Occasionally he used rationalization: without surgical treatment the patient will die; therefore, he has "nothing to lose" and "deserves a chance" to be cured. The tenuous character of such reasoning is obvious. When operation fails, the patient loses, and often it is his most precious possession, his life. In reality, he loses everything, the surgeon loses nothing.

How can the surgeon minimize the chances of rendering inappropriate or even harmful treatment? This goal can be approached by careful analysis of the problem preoperatively. Thus he might first consider the general factors which bear on management of a specific case: (1) The patient: Weigh carefully his condition and assess his ability to recover from the proposed treatment, the prognosis with and without treatment, the socioeconomic and emotional aspects and, of course, the desires of the patient and his family. (2) The disease: Review the natural history, possible and probable extent, curability with radical treatment, the effectiveness of palliative operation, and survival with nonoperative treatment. (3) The operative procedure: Consider carefully the magnitude of the exposure and tissue removal, stress, blood loss and necessary replacement, reconstitution of tissues, resultant physiologic and anatomic deficits, and the immediate and late risks of complications and death. (4) The surgeon, the anesthetist, and others: Experience, judgment, and proved ability command the highest premium and bear a direct relationship to the outcome. The surgeon would do well to assess his qualifications as objectively as those of the patient.

Next the surgeon should consider certain hypothetic situations most likely to be encountered and outline specific procedures and alternatives for each situation. The surgeon must "think the problem through" in order that his decisions will be founded on sound reasoning rather than intuitive or "snap" judgments. But such exercises require concentration, imagination, and abstraction and, human nature being what it

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[1]A word suggested by J. E. Schmidt, Charlestown, Indiana, in response to the author's request for a term opposite to "palliative."

is, the issues are not always spelled out in advance.

When things "go badly" after a palliative operation, and it is apparent that the patient has received no benefits, can it be said that the operation is truly palliative? Similarly, is an operation undertaken for cure truly curative if the patient later dies from metastatic cancer? The answer to both questions is no. But how should we designate operations which not only fail to achieve their objective but leave the patient worse than before? The word "cacotelic," meaning "tending to end badly," would seem appropriate in this context.

Harm to the patient is most likely to result from surgical inexperience and poor judgment, or when cancer is unexpectedly encountered, or sometimes when an intriguing new or more radical operation has become fashionable. Extended operations must be undertaken with great care. They are indicated only when there is reasonable hope that the lesion can be encompassed, that the patient can withstand the procedure, and that the benefits will be significantly better than those from a less radical operation. With a person suffering from the infirmities of aging and visceral cancer, the decisions are often difficult. Obviously there are no benefits to the patient if one cures the cancer but loses the patient postoperatively from a cerebral hemorrhage or similar catastrophe.

Generally, I believe operations are most likely to fail as the magnitude of the anatomic or physiologic deficit produced increases, and as the indications become less well-defined or established. For example, cordotomy in metastatic cancer, adrenalectomy or hypophysectomy for advanced breast cancer, hemipelvectomy for metastatic tumor, pelvic viscerectomy for spreading cervical cancer are likely to turn out badly and are rarely indicated. The most effective palliative operations are those which do not result in severe deficits or crippling and which promise immediately high dividends. For example, colostomy or enterocolostomy for irremovable obstructing cancer of the rectum or colon, simple mastectomy for smelly, ulcerating incurable breast cancer, cholecystoenterostomy for the obstructive jaundice of pancreatic cancer, and resection with anastomosis in selected cases of incurable cancer of the stomach and colon.

Palliative procedures are not always necessary and should not be undertaken indiscriminately. The patient with nonresectable cancer of the colon or rectum without obstruction may not be helped materially by a colostomy. Aside from the physiologic and social aspects of the problem, it is sometimes better to leave the alimentary canal intact because an external opening to relieve obstruction may never be needed. The same may be said of gastroenterostomy and feeding gastrostomy and jejunostomy for gastric cancer. There is little to be gained from a new opening for diversion, or a vent for feeding, when the ulcerating cancer remains. When obstruction is present there may be some rationale for these procedures, but the benefits are likely to be small and of short duration.

The treatment of cancer has many facets including carefully selected, timed, and executed operations. In general, operations become less important as cancer advances. The surgeon must be circumspect in his approach to these complicated problems. He should avoid those operations which are most likely to bring no benefit to his patient and which tend to end badly.

THE SURGEON AT WORK

A USEFUL TECHNICAL DETAIL IN THE PERFORMANCE OF GASTRIC RESECTION

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FOR MANY YEARS I have used a simple maneuver in gastric resections with the antecolic Billroth II type of anastomosis (Hofmeister modification) which has proved to be very useful for many reasons.

In Figure 1 it will be noted that the duodenal stump has been closed and the von Petz machine applied. The upper two-thirds of the stomach, from the lesser curvature to the greater curvature, is cut between the two rows of clips. The proximal row of clips has been inverted in a lock stitch of No. 00 chromic catgut and overlaid by a seroserous Lembert suture. The afferent loop of jejunum is then brought up from the ligament of Treitz anterior to the colon and is attached to the full width of the stomach from the greater curvature to the lesser curvature with interrupted sutures. The afferent loop should not be too long, and should be fairly taut. The gastrojejunal anastomosis is next accomplished in the usual

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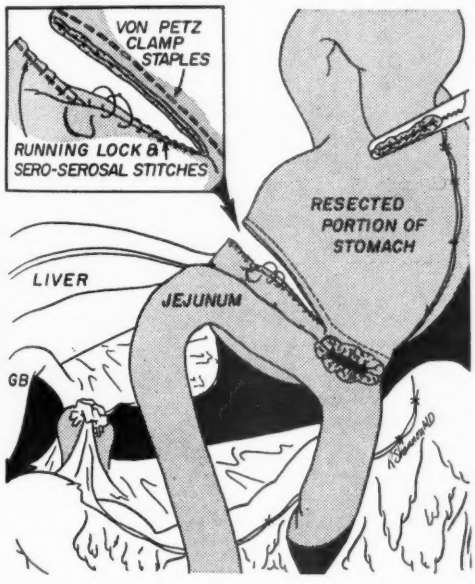

FIG. 1.

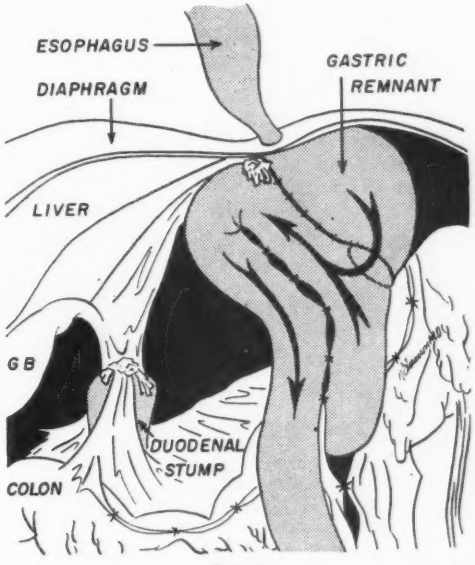

FIG. 2.

manner, allowing a one and one-half finger length stoma.

The descending loop of jejunum reaching from the lesser curvature to the greater curvature is then attached to the ascending loop with 3 or 4 sutures of interrupted atraumatic No. 000 catgut (Fig. 2).

This is not a new principle and no claim for originality is made. The Noble operation for chronic recurring intestinal obstruction and the plication of the ileum in ileostomy are based upon this principle. C. H. Mayo used it many years ago in the Balfour-Polya type of gastric resection in lieu of a jejunojejunostomy.

The advantages of this simple maneuver are that it prevents the otherwise floating descending loop from torsion, herniation behind the stomach, kinking at the junction of the ascending loop, and attachment to other parts of the abdomen causing intestinal obstruction. An added advantage is that it prevents the protrusion of the jejunal mucosa into the stomach causing stomal obstruction. It may be that the approximation of the afferent and efferent loops, by slowing up the filling of the jejunum, is responsible for the infrequency of the dumping syndrome which has been experienced in my patients.

AN INSTRUMENT FOR THE PREVENTION OF AIR EMBOLISM DURING DIRECT VISION CLOSURE OF ATRIAL SEPTAL DEFECTS AND MITRAL VALVULOPLASTIES

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EMBOLISM from air retained within the open heart has been recognized as a potential hazard in direct vision intracardiac surgery and various techniques have been suggested by Glenn, Miller, Nichols and their associates for its prevention. Closure of ventricular septal defects utilizing extracorporeal circulation is usually not complicated by the possibility of air embolization, if ordinary care is exercised, because with the patient supine the defect itself is usually uppermost in position and thus provides an excellent vent for air trapped within the beating left ventricle. If the ventricles have been arrested, their beat is restored before finally closing the defect. Occasionally, for technical reasons in patients with very small ventricular defects, we have completely closed the defect after filling the ventricle with 5 per cent glucose in distilled water before restarting the heart.

The closure of atrial septal defects, however, is associated with the potentiality of this complication unless suitable precautionary measures are adopted because air may be trapped easily in the left ventricle by the competent mitral valve and then be ejected into the aorta while the right atrium and atrial defect are still open and being worked upon.

A new instrument has been developed which simply and effectively obviates this problem of air entrapment in the left ventricle during the closure of atrial septal defects. This instrument is designed to keep the mitral valve incompetent throughout the septal defect repair and has been developed primarily for those cases in which a pump-oxygenator is used. Because of the unique design, the atrial septal defect may be completely closed before the instrument is removed from the left ventricle, and the mitral valve is then allowed to become competent again. Instillation of glucose or saline into the open heart, practices prone to complicate fluid balance, is unnecessary when this device is utilized. This instrument also has proved very useful for the same purpose in direct vision reparative procedures upon the mitral valve (3, 5–7) for stenosis or regurgitation. In these procedures, the left atriotomy may be completely closed before the spiral is removed from the mitral orifice.

The instrument is constructed of stainless steel spring wire (0.28 inch) and because of its configuration has been termed the "mitral spiral." In Figure 1 are shown the several sizes available for patients of varying age.

METHOD OF USE

The vessel cannulations are carried out in the usual manner and the patient is connected to the

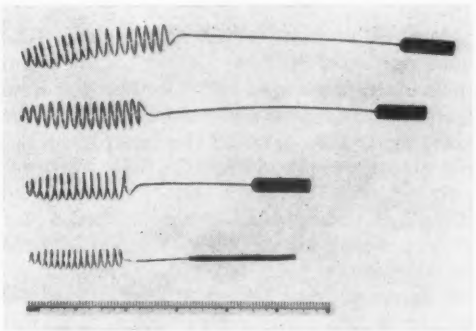

FIG. 1. The various sizes of mitral spirals that cover the range of heart sizes from children to adults.

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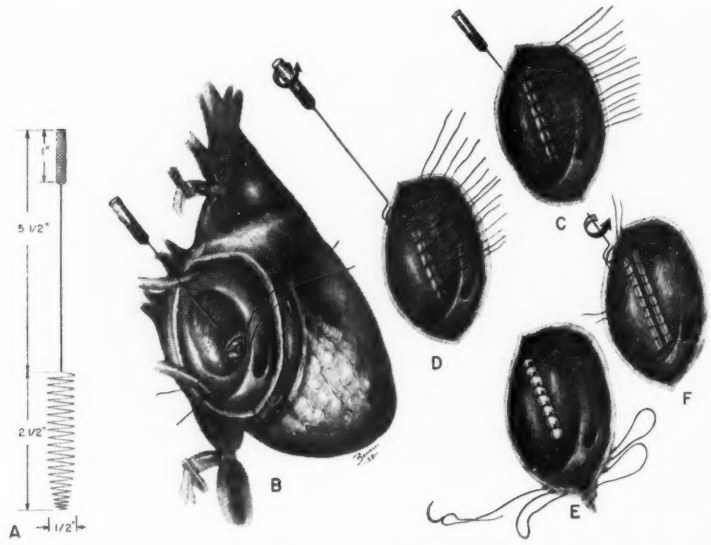

FIG. 2. Surgical technique for direct vision closure of atrial (secundum) defects utilizing the mitral spiral and extracorporeal circulation. A, Basic design of the instrument to render the mitral valve incompetent. B, As soon as the right atrium is opened the exploring finger is inserted through the defect into the left ventricle and a suitably sized spiral is guided into place. Additional blood then may be safely aspirated to expose the pathologic anatomy. Interrupted stitches of silk (No. 000) are placed. C, The stitches are all tied with the spiral still in place holding the mitral valve incompetent. The coronary sinus and bronchial return have been allowed to accumulate and completely fill the left side of the heart as the corrective stitches are tied. No additional glucose or saline is necessary. D, The spiral is rotated out of the heart. E, The margins of atrial septal defects are often remarkably attenuated so that a strip of compressed polyvinyl sponge has sometimes been laid on the suture line and the stitches have been retied over it. F, An alternative technique frequently utilized has been closure by placement of interrupted mattress stitches tied over two slender pledgets of compressed polyvinyl sponge. Again, the spiral is removed after the closure is complete.

pump-oxygenator (bubble type). The cardiopulmonary bypass is commenced and the right atrium is incised. The instrument is placed through the atrial septal defect into the left ventricle with a finger as a guide immediately following the routine exploration of the mitral valve. The spiral portion of the device maintains the mitral valve incompetent and only the thin wire stem protrudes through the septal defect. With the instrument in position, all the interrupted No. 000 silk sutures are placed (Fig. 2B). These sutures are then tied down (Fig. 2C) and as the last silk is tied, the left atrium is checked for the presence of air. No filling solution into the left side of the heart is required because the coronary sinus and bronchial artery blood returning to the left atrium is sufficient to fill this side of the heart and displace any air. Cardiac arrest is not utilized for atrial (secundum), atrioventricularis communis, or mitral valve surgery. After tying all sutures and closing the defect completely, the instrument is easily twisted out of the left side of the heart through the intact atrial septum (Fig. 2D and F). Because of its smooth corkscrew construction it is impossible for the instrument to become entangled in the mitral valve or chordae tendineae during its extrication from the left ventricle. After removing the instrument, the closure is often reinforced with a strip of compressed ivalon sponge, which is secured in place by retying the original interrupted sutures again (Fig. 2E). The right atriotomy is then closed with a running suture of No. 000 silk and the perfusion is terminated.

By use of this type of deliberate and precise technique made feasible by the pump-oxygenator, the surgical risk for correction of atrial defects has been less than 2 per cent (52 patients

operated upon with 1 death), and the cure rate to date in recatheterized patients has been 100 per cent.

DISCUSSION

During the direct vision closure of various types of atrial septal defects and mitral valvuloplasties utilizing the pump-oxygenator it is not necessary to arrest[1] the heart in order to obtain excellent exposure of the pathologic condition. Thus, there has been a sizable volume of blood returning to the atria during the cardiopulmonary bypass by virtue of coronary sinus flow and the bronchial arterial contribution. This flow into the open heart is beneficial since it frequently keeps the left side of the heart comfortably full of blood and thus helps prevent air entrapment in the left ventricle. Occasionally, the bronchial artery and coronary sinus return is minimal or an overzealous assistant attempts to aspirate with the cardiotomy sucker the returning blood so completely as virtually to empty the left ventricle in which case air entrapment in the left ventricle becomes a hazard. Therefore, as a routine practice we recommend that no more blood be sucked out of the left side of the heart than is necessary to visualize the pathologic condition accurately. However, with the mitral valve held incompetent by the spiral, the surgeon may have no fear of completely emptying the left side of the heart for as long as necessary to satisfy doubt about the presence of other or unusual lesions.

It has been easy to insert the instrument by guiding it along the exploring finger placed through the atrial septal defect and mitral valve into the left ventricle. It is important too, to mention that the size of the instrument chosen for a particular case be such that it can be positioned so that the spiral portion does not interfere with closure of the defect and only the thin wire stem should transgress the septal defect. The 4 instruments diagramed in Figure 1 appear to be satisfactory for virtually all sizes of hearts that we have encountered. With this device, atrial septal defects may be repaired either through an anterior bilateral thoracotomy or through a right posterolateral thoracotomy. If the patient is in the right lateral position, it is important to check carefully for trapped air in the much enlarged right pulmonary veins which are uppermost in this position.

As mentioned, this instrument offers the advantage of maintaining the mitral valve incompetent even after the atrial septal defect is completely closed or in the case of mitral valve surgery until after the left atriotomy is closed. The use of a large catheter or instrument placed into the left ventricle to hold the mitral valve open may not only impede good exposure but fail to offer complete protection against trapped air since the mitral leaflets can close competently around the catheter or shank of a forceps. Moreover, these instruments of necessity must be removed before the defect is completely closed.

The mitral spiral has been used by us in more than 100 patients undergoing total body perfusion with direct vision repair of atrial (secundum) septal defects, atrioventricularis communis, and mitral valve reconstructions without a single incidence of air embolism.

CONCLUSIONS

1. A new instrument has been developed which prevents the entrapment of air in the left ventricle during the closure of atrial septal defects or mitral valve surgery utilizing a pump-oxygenator.

2. This simple device maintains the mitral valve incompetent during the complete closure of the atrial septal defect and is removed through the intact septum after completion of the repair.

3. The instrument obviates the need for catheters or instruments in the left side of the heart and eliminates the use of solutions such as glucose or saline for air displacement.

4. The instrument has been equally useful in the open reconstructive procedures for mitral regurgitation or stenosis.

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A TECHNIQUE FOR INCREASING ABDOMINAL CAPACITY IN THE REPAIR OF MASSIVE VENTRAL HERNIA

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OMPHALOCELE is an uncommon but readily recognized congenital anomaly in which the abdominal viscera of the newborn are herniated into the base of the umbilical cord. Since death inevitably supervenes if the abdominal viscera are not promptly protected by cover of the normal structures of the abdominal wall, it is clear that this condition represents an emergency of the gravest sort.

Mortality can be directly correlated to the size of the abdominal defect. Gross has stated that the experience at the Children's Hospital in Boston demonstrates that: "In those patients with a sac less than 7 centimeters in diameter there is about a 75 per cent chance of survival following surgery. . . . When the sacs were larger than 9 centimeters, the survivals were reduced to about 15 per cent. Whenever a large portion of the liver was found in an omphalocele, a grave outlook could be expected."

The techniques by which repair may be effected have been adequately described in the literature. However, in many cases the disparity in size between an apparently underdeveloped peritoneal cavity and the huge mass of herniated organs may be such as to make complete reduction and repair of the hernia at the initial stage impossible. To cope with this larger deficit, Gross has popularized the so-called, "two stage operation." In this approach the membrane covered organs are first covered only by skin mobilized from the lateral aspect of the abdominal wall, and the ensuing hernia is definitively repaired as a second procedure. The ultimate repair of this hernia, however, may confront the surgeon with a formidable problem. The peritoneal space may remain inadequate, and, indeed, the initial surgery may have left a new set of problems despite its lifesaving role. If the dissection of skin to cover a large omphalocele has been inadvisedly carried over the chest wall, the infant is exposed to subsequent danger when the solid organs in the peritoneal cavity tumble outward and upward over the costal margin and come to rest partially outside the ribs. Technically, this situation is even more difficult to handle than that originally posed by the presence of the omphalocele. Gross alludes to the fact that he has seen this complication and mentions that, under these circumstances, the lower part of the thoracic cage is displaced posteriorly toward the vertebrae, eliminating the subphrenic fossa and making it impossible to replace the liver within the peritoneal cavity at a second operation. Since this problem, in his opinion, is almost insolvable, he cautions that at the first operation one should never free the skin up over the chest any further than is necessary to gain coverage of the omphalocele.

A technique is described herein by which a subphrenic space and an increased peritoneal capacity may be developed through a series of surgical procedures. This approach was designed and successfully utilized in a child who had a massive herniation and external displacement of the liver following extensive mobilization of skin to cover a large omphalocele.

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CASE REPORT

S. G., a white female child, was born on January 30, 1951, at the Johns Hopkins Hospital. There was immediately apparent an enormous omphalocele which presented through a large defect in the abdominal wall and which contained the liver, all of the small intestine, and the colon. She was operated upon immediately. The omphalocele could not be reduced and, therefore, first stage repair was carried out. Skin flaps were mobilized laterally to the vertebral column and in a cephalocaudad direction from the clavicles to the pubic symphysis, permitting the skin to be closed over the omphalocele. There was a small slough of the skin in the central portion of the repair, but during the next few months this healed. A tight binder was applied thereafter to the abdomen to obtain some reduction of the hernia.

At the age of 9 months, the child was taking feedings poorly, vomiting, and failing to gain weight. Accordingly, the binder was discontinued, and thereafter the ventral hernia appeared to get somewhat larger.

FIG. 1. Massive ventral hernia in a 23 month old child. The fullness of the superior portion of the hernia is due to the right lobe of the liver overriding the right costal margin.

When the child was 1 year of age, she was readmitted to the hospital for consideration of further treatment. On this admission, a respiratory infection developed, and she was again discharged to return to the hospital in September of 1952, at which time she was 21 months old. A long midline incision was made, and the skin was freed up from the liver which was lying entirely anterior to the right costal margin. When the liver was suspended only by its vessels and the common duct, it was still impossible to replace it into the abdomen. Accordingly, the skin was carefully tacked around the edges of the defect laterally and superiorly in the hopes that subsequent pressure by wrapping over the mass directly would effect enlargement of the peritoneal cavity. An appendectomy was carried out.

Shortly after discharge from the hospital, it was noted that the liver was again overriding the lower thoracic cage. There was no significant reduction in the size of the hernia which had grown to massive proportions (Fig. 1). It was feared that the unusual position of the liver jeopardized the patient's life. There had been some retardation apparent in her mental development, although she had gained in weight and stature.

The problem as visualized at this time involved the construction of a subphrenic fossa to accommodate the liver as a first step toward reconstruction of the abdominal wall. It was contemplated that by lowering the right costal margin and concurrently reattaching the anterior border of the diaphragm on the right at a higher level, sufficient subdiaphragmatic accommodation for the right lobe of the liver might be obtained. Respiratory function studies were carried out, and in view of the absence of any demonstrable respiratory limitation, it was decided that in all probability the child would be able to withstand any possible reduction of vital capacity ensuant upon these procedures.

On September 23, 1953, the first operation designed to attain these ends was carried out. Under ether anesthesia a long thoracoabdominal incision was made over the seventh rib extending down anteriorly over the abdominal cavity. The liver was again completely mobilized from the skin, costal margins, and diaphragmatic attachments. A striking finding was that of a 3 to 4 centimeter groove in the dome of the liver representing the point at which it had arched over the costal margin and been held captive for the 2½ years of the child's life. When the liver and intestines had been adequately freed, the seventh rib was resected subperiosteally for its full length. An incision was then made through its bed and through the costal margin, and a wedge of the costal margin was removed. This had the effect of hinging the lower portion of the right thoracic wall from the eighth rib downward only upon its vertebral attachments. It was possible to displace this flap downward and outward. The right side of the diaphragm was completely detached anteriorly. The seventh rib was then affixed between the sixth and the eighth ribs transversely to bridge this space using this rib as a strut to keep the hinged lower flap of thorax displaced downward and outward. Because of an infolding of the costal margin, it was necessary to fracture the costal margin in several places to allow it to relax. The right side of the diaphragm was then resutured onto this revised anterior chest wall, 1 inch higher at all points. It was then possible manually to reduce the liver to a normal position. The child was discharged on October 9, 1953.

Within 1 month it was apparent that the liver was maintaining its position well and that the right thorax was moving well with respiration. The child was well and vigorous. It was also noted that now the abdomen was definitely smaller on the right side than on the left. During the months which followed, the child developed very nicely. The apparent mental retardations seemed to wane and she began to talk and converse and to develop dramatically. However, recurrent fecal impaction began to occur. Repeatedly, enemas and manual removals of impactions were necessary. Because of the apparent success of the procedure on the right side it was decided to carry out a similar operation on the left side with the intent of increasing the capacity of the peritoneal cavity.

On February 27, 1954, the child was again submitted to surgery. It was possible at this time to palpate a rim of musculofascial tissue up to a level approximately 2 fingerbreadths above the pubis and well around on the flanks. It was estimated that the abdominal defect at this time extended from this rim up to the xiphoid and perhaps 9 centimeters from side to side. The incision on the left side was extended laterally from the xiphoid, and the eighth rib was resected. Again, the thorax was entered, the diaphragm divided anteriorly, and extensive dissection undertaken under the skin to free all the viscera which had encroached between the skin and the chest wall on the left side. The eighth rib bed having been divided, the ninth, tenth, eleventh, and twelfth ribs and the soft tissues between were displaceable in-

feriorly and laterally as a flap hinged at the vertebral angle. The eighth rib was inserted transversely between the seventh and ninth ribs anteriorly as a strut to keep this musculoskeletal flap properly positioned. The diaphragm was then resutured approximately 1 inch higher than its previous line of insertion on the parietes. It is interesting to note that there was at no time any evidence of phrenic nerve impairment. Upon completion, there was no longer any obvious overhanging of any abdominal viscus or organ upon the chest wall. The massive "interspace" created by the insertion of the strut was reinforced by a portion of the latissimus dorsi which was sutured over this. A considerable degree of postoperative distention followed this operation, but on the whole the child did rather well and she was discharged approximately 2 weeks postoperatively (Fig. 2).

Upon the completion of this second procedure and the ending of a satisfactory convalescence, it was believed that the immediate threat to the child's well being had been ended. However, between the latter portion of 1953 and the beginning of 1954 obstipation was an enormous problem, and it was necessary in August 1954 to readmit the child to the hospital for removal of a fecal impaction. Again, it was our decision to wait until normal growth processes would help to enlarge the peritoneal cavity somewhat.

In November 1954, examination was carried out under anesthesia. When sufficient pressure was made to reduce the hernia completely, the child seemed to experience extreme respiratory distress and, accordingly, further procedures were deferred at this time.

In March 1955, at which time the child was 4 years old, she was readmitted, still severely troubled by constipation and unable to defecate without multiple enemas. On March 10, 1955, under general anesthesia, much of the scarred skin over the abdominal wall was removed. The bowel was completely mobilized, and again the complete area which had been undermined at the time of the original operation was exposed, the skin being mobilized down to the level of the pubis, over the thorax, and onto the flanks. There was no longer any anterior displacement of the liver or spleen. Superiorly, the abdominal wall was bounded by the ribs; laterally, a ribbon, perhaps 1 inch wide, of muscle and fascia existed in the flanks. Inferiorly, a 3 inch wide musculofascial band extended to the pubic symphysis. The defect over which there was no abdominal wall was, therefore, approximately 10 by 15 centimeters. A large sheet of tantalum was sutured firmly to all edges of this defect with interrupted stitches of tantalum wire. This was done under moderate, although apparently not intolerable, pressure. At the completion of this procedure, the contours of the body appeared normal. The skin was tailored and the subcutaneous space drained. The child withstood the procedure well (Fig. 3). Figures 4, 5, and 6 show the significant changes after operation.

Two months later there was apparently some separation of the tantalum mesh on the left side inferiorly. At a 9 day hospitalization, the tantalum was resutured into position and the postoperative course was completely unremarkable.

For a period of 1 year after this, the child wore a corset. There has been no further difficulty with constipation. She attends school, has accepted a new child into the family perfectly well, and appears in every way to be a well adjusted, perfectly happy, normally developed little girl. At the time of this writing she is 7 years old and, when clothed, presents a completely normal appearance. On physical examination, there is a soft area over a portion of the tantalum. But most significant, perhaps, is the fact that the defect is not increasing at all in size and, if anything, seems to be diminishing. Certainly, the area of absence of abdominal wall is becoming increasingly less significant relative to the total size of the abdominal wall, and the musculofascial areas inferiorally and laterally are growing normally.

FIG. 2. Appearance of child, at 4 years of age, following the alterations of the rib cage and diaphragm. It is noteworthy that the superior portions of the massive hernia are flattened. The solid upper abdominal viscera have been returned to the subphrenic fossae.

DISCUSSION

When an omphalocele or congenital diaphragmatic hernia has been covered by skin alone, the

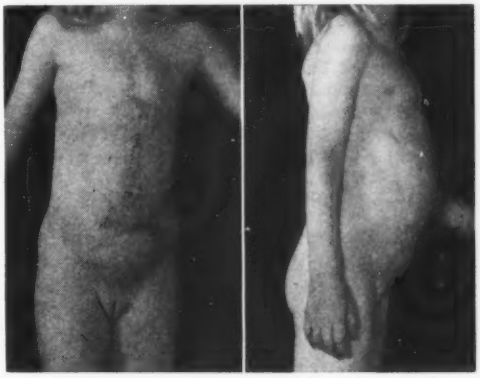


FIG. 3. Bodily contours of this child at 14 months after completion of hernia repair. Tantalum mesh has been utilized for support. The child has no ill effects from the large metallic screen or the costal and diaphragmatic revisions.

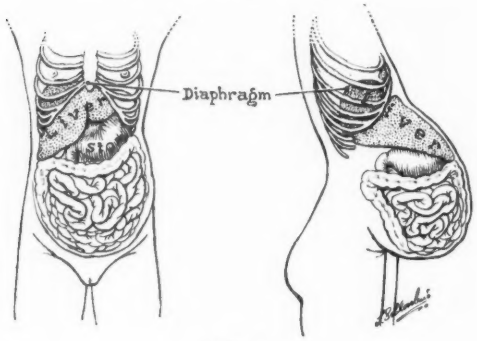
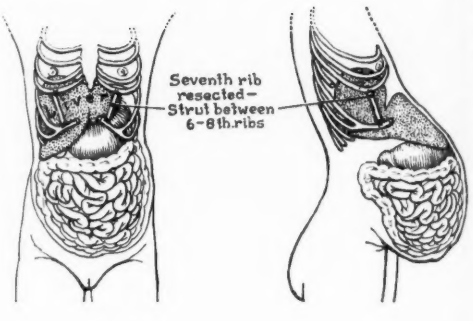


FIG. 4.



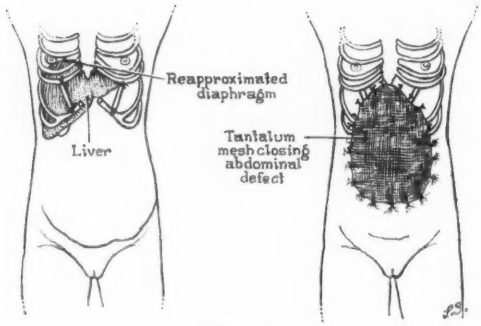


FIG. 6.

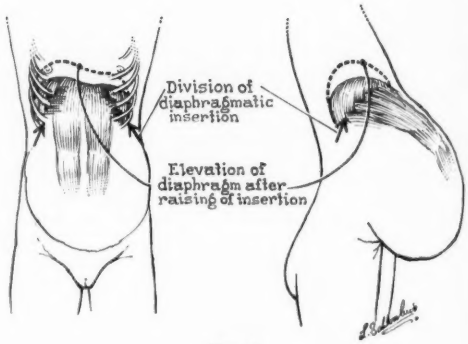


FIG. 5.

FIG. 4. Diagrammatic illustration showing the degree of herniation in the case presented. There is herniation of most of the intestine. The liver has projected outward from the subphrenic space and lies partially behind the ribs and partially anterior to them, and superior to the costal margin. A deep groove transverses the superior aspect of the right lobe of the liver. There has been significant decrease in the anteroposterior diameter of the chest.

FIG. 5. The total effect of the thoracoplastic procedures and diaphragmatic modifications is shown. On each side, the lower portion of the thoracic cage has been displaced downward and outward, using the resected rib as a strut to maintain position. Concurrently, the anterior insertion of the diaphragm has been severed and resutured at a higher level. The aggregate effect of these two maneuvers is to create a sizable space under the diaphragm, sufficient to accommodate the abdominal organs. These alterations were accomplished in two procedures, the right side completely first, and then the left side.

FIG. 6. Completion of the repair as a third operation. With the organs in normal position, tantalum mesh is secured to the edges of the defect with sutures of tantalum. The normal bodily contour is achieved, and support is afforded by this abdominal wall.

repair of the resulting ventral hernia may be most difficult if the peritoneal cavity remains inadequate in size to receive the abdominal organs.

It is incumbent upon the surgeon, however, to restore the herniated organs to a more normal position as soon as possible. The hazards of obstruction, strangulation, and impaction inherent in this situation are obvious. Beyond this, the prolapse of the liver poses another and apparently more subtle threat. The case presented herein is one of 2 children having similar difficulties. The second child was found dead in its crib under circumstances which were never adequate to account for its demise. Corrective surgery had not yet been undertaken, but the death served to underscore our own sense of urgency in this predicament.

Whether or not a peritoneal cavity actually increases in size without the stimulus of its nor-

mal contents to force its enlargement remains unclear. In any event, a situation which does not permit external pressure of a binder to reduce herniated organs through a defect automatically denies any stretching effect of these structures. In the presence of these large hernias there is apparently no increase in peritoneal size or increase in area of abdominal wall within the first months or even the first years after the child's birth. It seems apparent, therefore, that in order to repair these massive hernias it is necessary by artificial means to increase the size of the peritoneal cavity. The stretching procedures by pneumoperitoneum which have been advised by some for the repair of massive hernias in adults are ineffectual in these instances, even if one has the temerity to try them in an infant. The net effect would be the stretching of the skin overlying the hernia itself. Accordingly, some means must be employed for creating a subphrenic fossa to accommodate the liver and subsequently for manufacturing space in which the bowel may normally be contained.

The techniques already outlined developed such space by making a skeletomusculofascial flap consisting of the lowermost ribs and their interposed soft tissues. This was achieved by the resection of one rib and the liberation of the components of the lower thoracic wall leaving them hinged only posteriorly. The resected rib was then interposed as a strut designed to force this hinged flap downward and outward. The anterior diaphragm was transposed upward for an inch. The completion of these maneuvers allowed normal reduction of the liver and of the spleen, and eventually of the bowel. At another stage, tantalum mesh was sutured to bridge the remaining abdominal defect completely. These operations succeeded in accomplishing for our patient the following: (1) replacement of the liver and the spleen to their normal position, (2) a support for the abdominal wall so that relatively normal contours were re-established, (3) apparently sufficient support and strength in the abdominal wall to permit the child to defecate normally, and (4) coincidentally or not, a striking improvement in the physical and mental development to place her on a par with others of the same age.

While it is not fondly supposed that this child will be able to escape further surgery prior to adulthood, there is every reason to believe that ultimately it will be possible to carry out repair of a defect which will have been reduced to the proportions of the more usual ventral hernia.

This method, or some modification thereof, may conceivably have other applications in the repair of massive ventral defects postsurgically or otherwise created. While it is not remotely suggested that the sequence of steps herein outlined need of necessity be followed or need in any way be the optimum solution under other sets of circumstances, it is believed that the ultimate gains accomplished by these maneuvers provide a useful mechanism for what may otherwise be an insurmountable problem.

CONCLUSIONS

1. Massive omphalocele at birth may pose a formidable surgical problem because of a deficient abdominal wall, remediable only by two stage procedures as advocated by Gross.

2. In a contemplated two stage procedure, skin dissection in the first stage should be avoided over the thorax so as not to permit extraposition of the liver over the anterior chest wall with the ensuant difficulty in reduction and anteroposterior compression of the thorax.

3. A procedure is outlined by which subphrenic and peritoneal space was created for the repositioning of the liver and of other viscera.

4. This technique may have application in conditions involving other massive defects of the anterior abdominal wall, or in the cure of large ventral or incisional hernias in which the organs have apparently forfeited their right of domicile within the peritoneal cavity.

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THE CONCEALED INCISION FOR SURGICAL APPROACH TO THE UPPER HUMERUS

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THE SURGEON who has had occasion to approach the upper humerus for the purpose of eradicating a bone cyst, benign bony, or cartilaginous exostosis, or to perform some other elective surgical procedure has most certainly observed the poor cosmetic result. If not, he has probably operated upon only a few patients, with extreme luck and good fortune. A recent poll of the attending surgeons of the New York Orthopaedic Hospital has shown that approximately 100 patients with bone cysts in the upper humeral shaft have been operated upon at that institution, and only 2 surgeons thought they might have had an occasional narrow scar result therefrom. The great majority hastened to volunteer that the operative scars in the upper arm have been uniformly broad and that the greatest complaint of the patient has been the "horrible" appearance of the scar. Once the vertical scar has become broad it is too late to do anything constructive about it. The most enthusiastic and skilled plastic surgeons have tried excision with "plastic closure" of the wound followed by radiotherapy, with no improvement of the unsightly scar.

Most textbooks which illustrate approaches to bones or joints either show the most direct and safe route or the favorite approach of the particular author, with little regard for the possible poor cosmetic result. In search of an approach which would give the least offending skin scar, credit should be given to S. Donald Malton, former resident on the Plastic Surgery Service of The Presbyterian Hospital, New York, who suggested the incision to be described, which has been used by the author, or under his guidance, in 4 instances with excellent results. The incision was first used for curettage and packing of a large bone cyst occupying the upper one-third of the diaphysis of the humerus in the youngest patient, a 7½ year old female. The operation was performed on August 13, 1957. The oldest patient on whom it has been used was a 16 year old male. The resident, with my assistance performed this procedure, and it was generally agreed that the approach and entire operation was in no way hampered by the placement of the skin incision.

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I believe that it is, therefore, worthwhile to present the so-called "concealed" incision so that the least objectionable cosmetic results may be obtained in such cases.

PRINCIPLE OF SKIN INCISIONS

Webster disagreed with Kocher's vertical incisions across joints and noted that these often crossed Langer's lines. He stated: "The simplest rule for making incisions in the most favorable direction is to follow the natural wrinkle lines. These are usually recognizable on the face, the neck, at the wrist, the axilla, the groin, or the back of the knee."

THE CONCEALED INCISION

Since it is impossible to make a skin incision in the upper arm which will furnish adequate exposure for the entire upper half or third of the humerus and at the same time have no portion of it become widened and ugly, it was necessary to compromise. The visible part of the incision is placed in one of the normal wrinkle lines in the anterior axillary fold. This portion of the scar remains narrow and scarcely visible. It is perpendicular to the distal portion of pectoralis major muscle. The longer and more utilitarian portion of the incision is continued somewhat medially below the edge of the pectoralis muscle and then downward, and finally is curved anteriorly. This lower part, which represents perhaps two-thirds to three-quarters of the entire incision, is placed entirely on the medial aspect of the arm so that when the arm hangs at the side in the normal slightly internally rotated position of relaxation, none of the scar on the medial aspect of the arm or perhaps only the tip of the lower end will be visible. This portion will be broader than desired, but it remains concealed unless the arm is rotated outwardly.

FIG. 1.

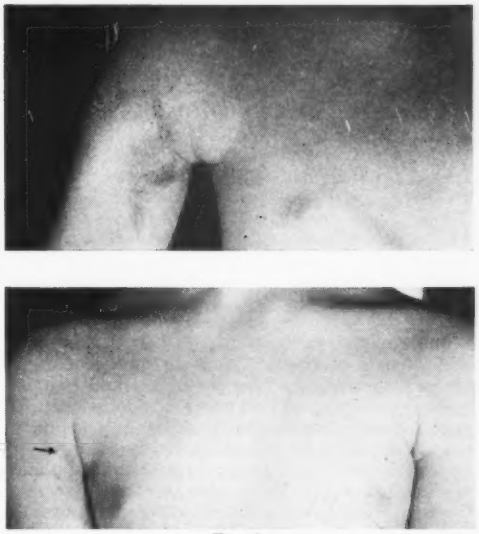

FIG. 2.

FIG. 1. A 12 year old girl had an operation upon the upper humerus through an anterior incision. This photograph was taken 5½ years later. Note the wide, ugly scar.

FIG. 2. Photograph of 7½ year old girl taken 5 months after operation for bone cyst of upper third of humerus (curettage and packing with bone chips) showing concealed scar. Above, the broad lower part of scar appears visible only with arm in external rotation. Below, at 8 months with arm in neutral position. Note that only the narrow upper part of the scar is visible in one of the axillary wrinkle creases. Compare with opposite side.

After the skin incision has been made, the deep fascia overlying the pectoralis major and biceps muscles is incised in the space between these muscles. The pectoralis muscle is then retracted in a proximal direction and the entire biceps (both heads) is retracted medialward. This is done with the shoulder slightly abducted and with the arm in external rotation. The neurovascular bundle is, therefore, not encountered. The only vessels encountered are the anterior circumflex which run in a lateral direction just below the surgical neck of the humerus. These may be clamped, divided, and ligated without harm being done. If one has difficulty in retracting the pectoralis major, the lower half of its tendon of insertion may be divided and later resutured. With very little additional retraction it is entirely possible to expose the shaft at a level immediately adjacent to the epiphysial plate.

At this stage, if the cyst wall is thin one may note the bluish color of the fluid within it as it shines through. The periosteum can be incised longitudinally and elevated and the roof of the cyst cut away sufficiently to permit complete exposure and curettage. Following definitive treatment of the cyst or other lesion, the periosteum may be resutured. Retractors are then removed and the pectoral and biceps muscles fall back into their normal relationship. If the pectoral tendon has been partially divided, it may then be repaired. The deep fascia is then loosely sutured, and the subcutaneous tissue and skin are closed in the usual fashion. Following the application of a sterile dressing, a soft pad is placed in the axilla and the arm is placed in a sling and loosely bandaged to the patient's chest. After 3 days, the dressing should be changed, and the patient may be permitted to start moving the arm. All skin sutures should be removed by the seventh postoperative day.

The accompanying illustrations of 2 cases are self explanatory. It is hoped that more surgeons will attempt to use this incision as it is believed that the improved results will be rewarding.

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THE SURGEON'S LIBRARY

Reviews of New Books

ALTHOUGH THE NAME of Charles Bell is familiar to medical men everywhere, it is doubtful if many of our profession realize how important and how extensive were his contributions to medical science. To recount those contributions, to honor him for them, and for the part he played in the founding of the medical school in which they themselves have played so important a part, Sir Gordon Gordon-Taylor, the distinguished surgeon, and E. W. Walls, the Courtauld Professor of Anatomy at the "Middlesex" have written the very interesting and informative biography *Sir Charles Bell; His Life and Times*.[1]

Bell entered upon his career with some unusual advantages: a gifted mother played an important part in his early education and handed down to her children, and particularly to Charles, a great talent for drawing. An older brother, John, the outstanding surgeon of his time in Edinburgh, trained him in anatomy and surgery; and another brother, George, who held the Chair of Scots Law in Edinburgh University, became his lifelong counsellor and guide, urging him to move to London when the path to advancement in Edinburgh seemed to be closed, and helping him throughout the difficult years with wise counsel and financial aid.

When Bell left Edinburgh in November 1804, at the age of 30, he had already gained a reputation as an anatomist from his published works, *A System of Dissections* and *Engravings of the Arteries of the Nerves and of the Brain*, both beautifully illustrated by himself. Though he had hoped to secure a position as assistant to one of the teachers in an important hospital, this hope was not realized. The unexpected leisure was not wasted, but spent in completing the plates for his *Essays on the Anatomy of Expression in Painting* which he had brought with him from Edinburgh. How important a contribution this was may be judged from the comments of Charles Darwin in the introduction to his own *Expression of the Emotions*. "Sir Charles Bell, so illustrious for his discoveries in physiology, published in 1806 the first edition, and in 1844 the third edition of his *Anatomy and Philosophy of Expression*. He may with justice be said, not only to have laid the foundations of the subject as a branch of science, but to have built up a noble structure. His work is in every way deeply interesting; it includes graphic descriptions of the various emotions, and is admirably illustrated. (He has) . . . shown the intimate relation which exists between the movements of expression and those of respiration. One of the most important points, small as it may at first appear, is that the muscles round the eyes are involuntarily contracted during violent expiratory efforts, in order to protect these delicate organs from the pressure of the blood. This fact . . . throws . . . a flood of light on several of the most important expressions of the human countenance."

To further his studies in anatomy and to house the models in wax of pathologic and anatomic specimens which he had begun to make already in his student days, Bell took an old house in Leicester Street and there began to take in "house pupils" to assist him in his dissections and in the necessary preparations for his lectures on anatomy and surgery for medical men, and on anatomy for painters. At the same time he began writing his *System of Operative Surgery*.

An event of this period, interesting for the light it sheds on the care of the war wounded, was his offer, accepted by the Medical Board, to go to Portsmouth to help care for the wounded returning from Corunna.

"The embarkation of Sir John Moore's troops from Spain had commenced a week or two earlier, following the memorable retreat which had closed with such a brilliant victory. At the time of their arrival at Haslar the wounded must have been in a very reduced state, with sepsis rampant amongst them; this aspect of the situation is borne out by the considerable collection of injured bones which Bell amassed at this period and which are preserved in his museum in the Royal College of Surgeons of Edinburgh. To the task of surgeon and pathologist Bell added that of artist, and a number of his magnificent paintings of the wounded which he then made, notably that of Opisthotonus, still form a notable part of his collection. Much of what he learned of gunshot wounds he acquired at this time and is embodied in his *Dissertation on Gunshot Wounds* published in 1814."

Again 6 years later, in June of 1815, immediately on hearing of the news of the battle of Waterloo he, with his assistant John Shaw, "their only passports being their surgical instruments" started for Brussels.

"For three days he continued his labours, his sleep reduced to an hour and a half in the twenty-four

[1]SIR CHARLES BELL; HIS LIFE AND TIMES. By Sir Gordon Gordon-Taylor, K.B.E., C.B., F.R.C.S., and E. W. Walls, M.D., Ch.B., B.Sc., F.R.S.(Ed.). 288 pages, 49 illustrations. $8.50. Edinburgh and London: E. & S. Livingstone Ltd.; Baltimore: The Williams & Wilkins Co., 1958.

hours; for spells of twelve and thirteen hours he operated without a break, until his arms were 'powerless with the exertion of using the knife'."

Early in 1812, Bell succeeded in securing possession of the well known school of anatomy in Great Windmill Street, founded by William Hunter and made famous by William and his brother John and their successors Baillie, Cruikshank, Wilson, and Brodie. From that time on Bell's success was uninterrupted. In 1814 he was elected to the staff of Middlesex Hospital, and with the new opportunities resulting from this appointment, the increasing number of students at the school of anatomy, and the increase in his private practice his future was assured.

The important *Idea of a New Anatomy of the Brain*, 'described by Neuberger at the Magna Charta of Neurology," was published in August 1811. Bell believed the cerebrum and cerebellum to have different functions, and that the nerves were composed of fibers differing in function, but "when he attempted to link the cerebrum exclusively with the anterior columns of the spinal cord and so with the anterior roots, and the cerebellum wi.h the posterior columns and posterior roots . . . he went astray."

The long drawn out controversy between Bell and Magendie is reported by the authors in considerable detail, and one cannot help agreeing with their conclusions that although Magendie discovered the functions of the spinal roots, "without Bell's work upon the nerve roots it is dubious if Magendie would have entered that field of enquiry at all, and had he done so might have found no light to guide his path."

The founding of the Middlesex Hospital Medical School and the important part which Bell played in its organization, his happy married life, his decision to accept the invitation from his Alma Mater to occupy the vacant chair in surgery at Edinburgh, and his final years in Edinburgh are recounted in a most interesting fashion.

A chapter (VII) which pictures vividly the world, and particularly the Britain, "into which Charles Bell was born," another chapter (IX) entitled "Surgical Practice in the Times of Charles Bell," an appendix which includes many interesting documents, notes of cases of gunshot wounds, a reproduction of the *Idea of a New Anatomy of the Brain*, as well as a number of illustrations which supplement the beautiful halftones spaced throughout the volume, all help to make this biography a treasure house for every reader who would know more about the history of an illustrious profession and the men who made it so.

—Sumner L. Koch.

VOLUME I of *Treatment of Cancer and Allied Diseases*,[2] the first of nine, covers the principles of treatment and represents the contributions of the editors and 55 others. The volume is extensively illustrated and contains a large bibliography. The initial chapter covers cancer prevention, organization of the tumor clinic, of cancer detection facilities, and of a program for home care. This is followed by an excellent chapter on diagnosis and pathology. The remainder of the volume is allocated to surgical irradiation, hormonal therapy, and chemotherapy. The fields of adjuvant therapy in surgery approximate the presentations in standard works on surgery. The chapter on vascular surgery pertaining to the treatment of malignant neoplasms, written by Welch and Miller, is outstanding. The extensive space allotted to irradiation is perhaps of interest to radiation therapists. Chemotherapy is briefly presented. The chapters on hormone therapy present considerable duplication and are very general. The reader is not provided with any clear program with which to solve the many admittedly confused endocrinologic therapeutic problems. No doubt the subsequent volumes, assigned to specific lesions, will provide detailed therapy in more specific terms.

—Clarence J. Berne.

THE COMPACT VOLUME of 347 pages entitled *Lesions of the Lower Bowel*[3] is literally "packed" with the results of the author's many years of experience at the Mayo Clinic. The profession is slowly (much too slowly) awakening to the fact that proctosigmoidoscopy remains a sadly neglected procedure in physical diagnosis. Jackman has presented this subject in such a manner that generalist, internist, surgeon, and proctologist can and should make better use of this diagnostic method.

Illustrations are well reproduced. Especially attractive is the color atlas of 75 plates. The excellence of the color plates more than offsets the slight inconvenience of referring back to a specific plate mentioned in the text.

The author portrays diagnosis and differential diagnosis of intrinsic, intramural, and extrinsic or extrarectal lesions of the terminal portion of the lower bowel—a very practical teaching method. His presentation of such important subjects as chronic ulcerative colitis, diverticulosis, diverticulitis, polypoid disease, and cancer leaves the careful physician no excuse for failing to recognize these conditions.

The reviewer is especially pleased with the presentation of extrarectal lesions, which, although not common, are often overlooked by the less experienced physician.

Students, house officers, and physicians who deal in any way with diseases of the large bowel will find this book an essential addition to their libraries.

—J. Peerman Nesselrod.

THE 1957 EDITION of the *Collected Papers of the Mayo Clinic and the Mayo Foundation*[4] continues the tradition of reflecting current practice at the Mayo Clinic in the many different fields of medicine. The large number

[2]TREATMENT OF CANCER AND ALLIED DISEASES; PRINCIPLES OF TREATMENT. Edited by George T. Pack, M.D., F.A.C.S., and Irving M. Ariel, M.D., F.A.C.S. 2nd ed., Vol. I. 646 pages, 505 illustrations. $22.50. New York: Paul B. Hoeber, Inc., Medical Book Dept. of Harper & Brothers, 1958.

[3]LESIONS OF THE LOWER BOWEL. By Raymond J. Jackman, M.D., M.S. 347 pages, illustrated. $15.50. Springfield, Ill.: Charles C Thomas, 1958.

[4]COLLECTED PAPERS OF THE MAYO CLINIC AND THE MAYO FOUNDATION. Editorial Staff: Carl M. Gambill, A.B., M.D., M.P.H., James R. Eckman, A.B., M.A., Ph.D., M. Katharine Smith, B.A., Florence L. Schmidt, B.S.E., George G. Stilwell, A.B., M.D., and Guy Whitehead, B.A., M.A., Ph.D. Senior Consultants: Richard M. Hewitt, B.A., M.A., M.D., and John R. Miner, B.A., ScD. Compiled by George G. Stilwell, A.B., M.D. Vol. 49-1957, 827 pages, illustrated. $13.00. Philadelphia and London: W. B. Saunders Co., 1958.

of patients available for study lends more than usual authority to the clinical conclusions, and the opinions expressed in the essays are, for the same reason, practical and realistic.

The new typography has added to the readability of the volume, and the index of authors has been altered so as to permit more space for the textual material.

In the papers relating to the practice of surgery, no controversial issues are discussed. Those dealing with direct vascular surgery and cardiac surgery maintain their practical and objective character. A comprehensive essay on the functioning carcinoid tumors and their remarkable hormonal manifestations is of special interest.

In the field of medicine, suitable emphasis has been placed on the cardiovascular system and its disorders. The various cerebrovascular insufficiency syndromes are well delineated and their management clearly discussed. There is unnecessary repetition on the subject of temporal arteritis. It receives important discussion in 4 separate papers. Much concentrated useful information on a wide variety of subjects is presented.

For those interested in having available in convenient form the results of careful studies of many patients by outstanding clinicians, this volume can be well recommended. —*John Farr.*

IN THE WORDS of the authors' preface, their text *Leukemia*,[5] presents "a fairly comprehensive picture of the present state of our knowledge (some might say ignorance) of leukemia." For, aside from generally good but shorter coverage of the subject in standard textbooks of hematology, the present work does represent the first good survey of leukemia since Forkner's monograph some 20 years ago. Beginning with an interesting, satisfactorily brief history of the disease there follows a delineation of the problems of leukemia from definition and etiology, through pathology and diagnosis, to present day concepts of therapy. The text is readable, bearing here and there the stamp of the inimitable literary style of the senior author; there are few typographic errors, the reproductions are excellent, and the indexing is satisfactory.

In general, the faults of the book are minor. The introduction of a section devoted to the course and special pathology of leukemia as related to symptomatology is somewhat novel but leads to a degree of redundancy when subsequently similar material is covered in a more orthodox fashion. The section on the relationship of leukemia to the myeloproliferative disorders serves as a sounding board for more recently espoused concepts of the authors, certain portions of which, though thought-provoking, are not necessarily in line with the experience of other research or practicing hematologists. Further, one wonders why so much text is devoted to this problem when relatively little is given to a discussion of the relationship of lymphocytic leukemia to the lymphomas. With minor variations in drug schedules, this reviewer is in agreement with the presented therapeutic concepts, though I doubt that all would agree with the "myelostimulatory" concept of the action of ACTH. This book is strongly recommended to all those with an interest in hematology.
—*Walter A. Rambach.*

BLACKBURN AND LAWRIE'S *Textbook of Surgery*[6] became available in July of 1958. As in most textbooks today, additional authors have contributed selected chapters, a feature which usually promotes more detail and comprehensiveness of the particular subject. Nevertheless, in this textbook which is primarily for students, short, direct, plain statements are used in each chapter.

This textbook represents the pattern of teaching of one hospital, namely Guy's Hospital in London. The direct, terse statements by the authors tend to give the general principles and exclude operative detail, and in many instances management detail has been sacrificed.

The authors must be congratulated for their success in adhereing to concise statements through all the chapters in their attempt to give a basic understanding of surgical practice. If long, detailed discussions of subjects, possibilities and probabilities, and changing pictures so evident to the teacher are tossed in detail to the student one cannot expect him to have a clear understanding of the subject matter. Some basic statements are a better starting point for the introduction to such subjects. This is well exemplified in the chapter on shock and the chapter on disturbances of water and electrolyte metabolism.

This book includes a particularly informative chapter on diagnostic radiology of the abdomen, a subject usually not clearly nor precisely presented in most textbooks. The chapter on principles of anesthesia is excellent for the introduction of this subject to the medical student. Many discussions of differential diagnosis are unusually well presented.

This book should prove interesting reading to any teacher because of its many concise, direct statements without embellishments. After going through page after page of well stated principles, one cannot help but give thought and consideration to the fact that this type of book could be sufficient for the medical student's introduction to surgery. Details as to management, therapy, and operative details could be given later. The authors have not intended it to be a book for reference in the management of surgical diseases.
—*R. Russell Best.*

THE MONOGRAPH entitled, *Medulloblastoma*,[7] is a thorough review of one of the most intriguing of the gliomatous tumors of the brain. It is written in two parts. Part 1, comprising slightly more than one-third of the volume, consists of pathologic considerations of neoplasia in general and medulloblastoma in particular. Special attention is given to the relation of medulloblastoma to other neoplasms, to the theories of its origin, and to its life history.

[5]LEUKEMIA. By William Dameshek, M.D., and Frederick Gunz, M.D., Ph.D. 420 pages, 142 illustrations. $15.75. New York and London: Grune & Stratton, Inc., 1958.

[6]TEXTBOOK OF SURGERY. Edited by Guy Blackburn, M.B.E., M.Chir., F.R.C.S., and Rex Lawrie, M.D., M.S., F.A.C.S., M.R.C.P. Foreword by Sir Russell Brock, M.S., F.R.C.S., F.A.C.S. (Hon.). 1122 pages, illustrated. $16.75. Springfield, Ill.: Charles C Thomas, 1958.

[7]MEDULLOBLASTOMA. By Benjamin L. Crue, Jr., LCDR, MC, USN. 206 pages, 17 illustrations. $5.75. Springfield, Ill.: Charles C Thomas, 1958.

Part 2 is an excellent summary of the clinical aspects of this tumor. By the amalgamation of statistics from many clinics, the author is able, perhaps for the first time in one place, to bring out a satisfactory picture of the age distribution and sex incidence of this lesion. The subjects of symptomatology, diagnosis, differential diagnosis, and treatment are very adequately handled, with special emphasis on radiation therapy. Consideration is also given to the possible uses of isotopes, chemical toxic agents, antibiotics, and hormones in attempts to control this as yet inoperable, incurable neoplasm.

The extensive 12 page, 401 item bibliography will be of value to the student of this lesion and of intracranial tumors in general. The book, though written mainly from the neurosurgical viewpoint, will certainly be of interest to the neurologist and the pediatrician as well as the neuropathologist and the neurosurgeon.

While it is an exhaustive review of the subject, the book is stimulating, rather than exhausting, to read. This reviewer cannot help but agree with the final single sentence paragraph of the work: "Medulloblastoma remains today as one unsolved challenge."

—*Hale Haven.*

SINCE THE ADVENT of the first edition in 1937, Saphir's *Autopsy Diagnosis and Technic* has admirably filled the need for a concise yet suitably comprehensive publication of this type.

The fourth edition,[8] published 21 years later, brings the material up to date. In the space of less than a hundred more pages, new chapters on history; handling of bodies exposed to, or treated with radioisotopes; and, tissue banking techniques, have been added. The same brief and concise style used in the past is followed. In addition, the sections on stillbirths, infants, and diseases of the breast have been enlarged. The chapter on "Do and Don't—Certain Suggestions for Quick Orientation" based on the author's personal experience, remains an invaluable one.

The binding is sturdy and the format, practical and pleasing to the eye. This remains a very thorough handbook for necropsy procedure and gross interpretation.

—*M. G. Wheelock.*

ORVAR SWENSON'S object in writing the textbook, *Pediatric Surgery*,[9] was to "supplement rather than to duplicate volumes on general surgery" and "to describe the lowly simple abnormalities in an attempt to be helpful to the young surgeon, and to aid such harassed house officers and students, many simple procedures are described in detail."

In the foreword, William E. Ladd quoted Sir Lancelot Barrington Ward's statement, "The adult may safely be treated as a child, but the converse can lead to disaster." Ladd concludes with this excellent sentence, "This book should be of the greatest value to every surgeon performing pediatric surgery and of much interest and value to teachers of surgery, pediatricians, and general practitioners, who find it ever more difficult to keep abreast of the times in a constantly changing field."

Reviewing and studying this book has been a real privilege and pleasure. I believe Swenson has achieved his objectives, and I heartily agree with quotations given in Ladd's foreword.

The text contains 38 chapters on pediatric surgical problems and methods of treatment. The preparation of the patient emotionally as well as physically, gastric and intestinal suction, chemotherapy, and postoperative care makes up the important third chapter. There are many excellent photographs and illustrations; in some instances more descriptive labeling would be helpful.

The chapters on Hirschsprung's disease and those concerning the genitourinary system are exceptional. Much is the author's original work, for which he is to be commended.

—*Egbert H. Fell.*

THE SECOND EDITION of *A Manual on Cardiac Resuscitation*[10] should be read by every anesthesiologist and doctor who has anything to do with surgery. This clear, concise, 200 page, well illustrated manual, if studied and followed, will prevent many cardiac arrests. Those who have benefited by studying this book will understand the fundamentals of cardiac resuscitation, and will be better able to cope with cardiac arrest or a ventricular fibrillation when it occurs.

Discussions concerned with the causes, prevention, and treatment are excellent. Improper preoperative medication and rapid induction of an anesthetic are 2 of the many practical and well documented problems that the anesthesiologist and surgeon must understand and correct so as to prevent this cardiac emergency.

The steps in cardiac resuscitation are well covered. They are: (1) to re-establish the oxygen system and (2) to restore the heart beat. Reasons for failure of cardiac resuscitation are mainly three: (1) lack of a plan; (2) failure to act within the time limitation, and (3) severe inherent cardiac disease. "Things To Do" and "Things Not To Do" to develop a plan of attack and attain successful results are well presented.

This manual is recommended for study to all surgical and anesthesia residents and their seniors.

—*Egbert H. Fell*

AS INDICATED in Volume II of *Medicine and the Navy 1200–1900*,[11] following its decline under Charles I, the British Navy (and to a lesser extent its medical service) manifested a resurgence under the Commonwealth, the Protectorate, and the later Stuarts. The medical service for its part developed into a corporate organization based on the demands of the sea.

After the beginning of the eighteenth century, naval surgery began to hold its own as a profession, with an *esprit de corps* which assured a continuity of service previously unknown. The advent of hospital ships would have been impossible but for this change, and

[8] AUTOPSY DIAGNOSIS AND TECHNIC. By Otto Saphir, M.D. Foreword by Ludvig Hektoen, M.D. 4th ed. 549 pages, 80 illustrations. $8.50. New York: A Hoeber-Harper Book, 1958.

[9] PEDIATRIC SURGERY. By Orvar Swenson. Foreword by William E. Ladd. 750 pages, 980 illustrations. $20.00. New York: Appleton-Century-Crofts, Inc., 1958.

[10] A MANUAL ON CARDIAC RESUSCITATION. By Robert M. Hosler, M.D., F.A.C.S. 2nd ed. 208 pages, 17 illustrations. $5.50. Springfield, Ill.: Charles C Thomas, 1958.

[11] MEDICINE AND THE NAVY 1200–1900. By J. J. Keevil. Vol. II, 1649–1714. 331 pages, illustrated. $8.50. Edinburgh and London: E. & S. Livingstone Ltd.; Baltimore: The Williams & Wilkins Co., 1958.

with their institution under William III and Anne there came a furtherance of the concept of sea surgeons. With the intermingling of surgeons aboard hospital ships came the opportunity for interchange of ideas, with the expected advance of navy medicine both from clinical and administrative aspects.

Nevertheless, lacking true organization as a medical department, with no medical commandant, and no chain-of-command, the medical service remained something of an abstraction. Its progress despite such a nebulous framework is a tribute to the efforts of many naval surgeons whose names have long since become blended in mutual anonymity.

Keevil's two volumes bring together an astounding mass of information, which would undoubtedly have been lost except for his endeavors. The works read like textbooks, for such indeed they are.

—*C. A. Broaddus, Jr.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Textbook of Surgery. Edited by H. Fred Moseley, D.M., F.A.C.S., F.R.C.S.(Eng.), F.R.C.S.(C). 3rd ed. 1336 pages, 738 illustrations and 108 color plates. $17.00. St. Louis: The C. V. Mosby Co., 1959.

The Surgeon's Tale; the Story of Modern Surgery. By Robert G. Richardson. 278 pages, 45 illustrations. $4.95. New York: Charles Scribner's Sons, 1959.

Traitement des suppurations urétro-génitales et de leurs complications chez l'homme et chez la femme. By Pierre Durel and André Siboulet. 168 pages, illustrated. 2.100 fr. Paris: G. Doin & Cie, 1959.

Experimentation in Man. By Henry K. Beecher, M.D. 80 pages. $3.50. Springfield, Ill.: Charles C Thomas, 1959.

Surgery of the Stomach and Duodenum; A Handbook of Operative Surgery. By Claude E. Welch, M.D., D.Sc. (Hon.). 3rd rev. ed. 405 pages, illustrated. Illustrated by Muriel McLatchie Miller. $9.75. Chicago: The Year Book Publishers, 1959.

Atti della societa Lombarda de Scienze Medico-Bilogiche. Vol. XIII, Suppl. 208 pages, illustrated. Milan: Edizioni Minerva Medical, 1958.

Modern Trends in Diseases of the Vertebral Column. Edited by Reginald Nassim, B.M., F.R.C.P., and H. Jackson Burrows, M.D., F.R.C.S., 203 pages, 172 illustrations. $15.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1959.

Cirugia del cancer del colon y del recto. By Drs. J. Pi-Figueras and V. Artigas, P. Anfres, and A. Gimenez-Salinas. 562 pages, 314 illustrations. Barcelona, Madrid, Buenos Aires, Mexico, Caracas, Bogota, and Rio De Janeiro: Salvat Editores, S.A., 1958.

Atlas of Tumor Pathology. Section XII, Fascicle 40—Transplantable and Transmissible Tumors of Animals. By Harold L. Stewart, M.D., Katharine C. Snell, M.D., Lucia J. Dunham, M.D., and Samuel M. Schlyen, M.D. Published by the Armed Forces Institute of Pathology Under the Auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences—National Research Council. 378 pages, 287 illustrations. $3.50. Washington, D. C.: Armed Forces Institute of Pathology, 1959.

Dental-Medical Emergencies and Complications. By Ira Jay Berlove, D.D.S., M.D. 380 pages. $7.50. Chicago: The Year Book Publishers, Inc., 1959.

Lehrbuch der Geburtshilfe. By Prof. Dr. Heinrich Martius. Assisted by Prof. Dr. H. Hartl and Kathe Droysen. 4th ed. 731 pages, 768 illustrations. $14.20. Stuttgart: Georg Thieme Verlag, 1959.

Quadri Arteriografici. By Edmondo Malan. With the collaboration of G. Tattoni, C. Malchiodi, G. Bounous, and U. Ruberti. 124 pages, 81 illustrations. L. 5000. Torino: Edizioni Minerva Medica, 1958.

Newer Concepts in Clinical Proctology. By Frank D. Stanton, D.O. 364 pages, 124 illustrations. Sharon, Massachusetts: Frank D. Stanton, D.O., 1958.

Therapeutic Radiology; Rationale, Technique, Results. By William T. Moss, M.D. 403 pages, 146 illustrations. $12.50. St. Louis: C. V. Mosby Co., 1959.

The Physiopathology of Cancer. Edited by Freddy Homburger, M.D. 2nd ed. 1180 pages, 189 illustrations. $32.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1959.

Surgery of the Prostate. By Henry M. Weyrauch, M.D., F.A.C.S. 535 pages, 288 illustrations. $15.00. Philadelphia and London: W. B. Saunders Co., 1959.

Cancer; Diagnosis and Treatment. Edited by John B. Field, M.D., Ph.D. With 28 contributors. 796 pages, illustrated. $18.50. Boston: Little, Brown & Co., 1959.

Traité de technique chirurgicale. By B. Fey, P. Mocquot, S. Oberlin, J. Quenu, P. Truffert, M. David, M. Iselin, R. Dossot, R. Dubau, Ch. Dubost, Ct. Dubost, J.-J. Galey, Y. Longuet, J. Loygue, J. Mathey, R. Palmer, J. Perrotin, J.-C. Rudler, G. Thomeret, and J. Varangot. 2nd rev. ed. Vol. VII. 769 pages, 526 illustrations. 7,200 fr. Paris: Masson et Cie, 1959.

Les lesions traumatiques de l'uretère. By Jean Cibert and Michel Revol. 281 pages, illustrated. 4,200 fr. Paris: Masson et Cie, 1959.

Gynaekologische Zytodiagnostik. By Dr. Hans Igel. Foreword by Prof. Dr. H. Kraatz. 86 pages, 73 illustrations. Berlin: Walter De Gruyter & Co., 1959.

Die Laparoskopie und die Culdoskopie in der Gynaekologie. By Dr. H. Frangenheim. 70 pages, illustrated. $4.20. Stuttgart: Georg Thieme, 1959.

The Investigation of the Relative Function of the Right and Left Lung by Broncho-Spirometry; Technique, Physiology, and Application. By Frank Bergan, M.D. 145 pages, 85 illustrations. $4.50. New York and London: Grune & Stratton, Inc., 1958.

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Instrumentation in Anesthesiology. By William H. L. Dornette, M.D., and Verne L. Brechner, M.D. 242 pages, 130 illustrations. $8.00. Philadelphia: Lea & Febiger, 1959.

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PRELIMINARY PLANS FOR THE 45th CLINICAL CONGRESS CONVENTION HALL, ATLANTIC CITY, NEW JERSEY SEPTEMBER 28 TO OCTOBER 2, 1959

RETURNING to Atlantic City, New Jersey, for the third time, the Clinical Congress of the American College of Surgeons will again have headquarters for meetings and exhibits at Convention Hall on the famous boardwalk, with some sessions at nearby hotels.

General plans for the Congress follow those of previous years, and the program will be detailed in this Journal as it develops.

The medical student participation program, now in its fourth year, will have representatives from 36 medical schools in Illinois, the East, Canada, and Puerto Rico. Selected by their classmates, the students will follow a week-long schedule of activities planned by a College Committee headed by Dr. George V. Brindley.

Committee on Arrangements

Dr. Stuart Z. Hawkes, Newark, is Chairman of the Advisory Committee on Local Arrangements. Dr. Robison D. Harley, Atlantic City, is Secretary. Fellows of the College from New Jersey serving under Dr. Hawkes are:

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BENJAMIN DAVERSA, Spring Lake
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Dr. Carl A. Smith, Assistant Professor of Surgery, New York University College of Medicine, New York, and Dr. J. Garrott Allen, Professor of Surgery, University of Chicago, and Chairman of the College's Committee on Television, are in charge of the television program.

Official Evening Meetings

On Monday evening, September 28, Dr. Stuart Z. Hawkes will welcome visitors to the Congress, special guests will be introduced by Dr. I. S. Ravdin, and Dr. Dean Rusk, President, Rockefeller Foundation, will give the Martin Memorial Lecture. At the Friday Evening Convocation, Initiates will be presented for

fellowship, honorary fellowships conferred, and new officers inaugurated. Dr. Owen H. Wangensteen, incoming President of the College, will give the Presidential Address.

Television, Ciné Clinics, Motion Pictures

Bellevue Hospital, New York, will be the source of the famous closed-circuit operative telecasts bringing surgery as it is performed to Convention Hall viewers. The television program is produced by Smith, Kline & French Laboratories of Philadelphia. The Ciné Clinics sponsored by the Surgical Products Division of American Cyanamid Company, under the chairmanship of Dr. Hilger Perry Jenkins, Chicago, and the College's Motion Picture Committee, will include films made for this Congress. As in the past, committee-approved medical motion pictures will be presented throughout the week; the popular evening Motion Picture Symposium, consisting of short films of unusual interest, will be another event.

Postgraduate Courses

Among the nine Postgraduate Courses this year is one devoted entirely to athletic injuries. Because of the popularity of these seminars, early registration is recommended. Admission will be by ticket only. Courses and their chairmen are:

Preoperative and Postoperative Care of the Surgical Patient. CHAMP LYONS, Birmingham.
Gastrointestinal Disease. ROBERT T. TIDRICK, Iowa City.
Diseases of the Liver, Biliary Tract, and Pancreas. HARWELL WILSON, Memphis.
Cardiovascular Surgery. HENRY T. BAHNSON, Baltimore.
Athletic Injuries. DONALD B. SLOCUM, Eugene, Ore.
Gynecology and Obstetrics. BERNARD J. PISANI, New York.
Internal Fixation and Operative Treatment of Fractures. WILLIAM H. CASSEBAUM, New York.
Surgical Aspects of Pulmonary Disease. ROBERT R. SHAW, Dallas.
Problems in Pediatric Surgery. C. EVERETT KOOP, Philadelphia.

Forum

The Forum Committee, headed by Dr. Harris B. Shumacker, Jr., Indianapolis, will present approximately 250 reports covering the latest research, changes, and advances in surgical technique. The program again includes 16 general and 6 specialty sessions.

Baxter Lecture and Oration on Trauma

The third annual Baxter Lecture will be given by Dr. David Paton Cuthbertson, director of the Rowett Research Institute, Bucksburn, Scotland. The twenty-seventh annual Trauma Oration will be given by Dr. R. Arnold Griswold, Louisville, a past chairman of the College's Committee on Trauma.

Scientific and Industrial Exhibits

The Scientific Exhibition Committee will display informative exhibits showing results of recent study by research teams and surgical departments from medical centers.

Mr. Thomas E. McGinnis, Assistant Business Manager for the Clinical Congress, is in charge of Industrial Exhibits, and all inquiries regarding applications and space may be addressed to him at the American College of Surgeons' Chicago Headquarters, 40 East Erie Street, Chicago 11.

Advance Registration

Fellows are now receiving the Clinical Congress Invitation Brochure, containing information about hotels, Postgraduate Courses, travel, and registration forms. This is available to non-Fellows upon request. Early registration is strongly recommended for first choice at courses, hotel, and travel accommodations. Anyone registering in advance will find his badge awaiting him upon arrival at the Congress and will avoid delay.

Fellows whose dues are paid to December 31, 1958, pay no registration fee; those whose dues are not paid as of above date pay $40.00. Non-Fellows will pay $40.00 if registered Sunday, Monday, or Tuesday; $30.00 if registered Wednesday; $20.00 if registered Thursday; $10.00 if registered Friday. Members of the federal services will pay half of the above schedule of fees. No fee (except for Postgraduate Courses) is required of Initiates, members of the Candidate Group, and surgical residents. However, everyone who attends a Postgraduate Course pays a fee of $5.00.

Wives Invited

The Ladies' Entertainment Committee, under chairmanship of Mrs. James H. Spencer, Newton, and Mrs. Paul Mecray, Jr., Camden, is planning a week of unusually pleasant activities, and doctors' wives are cordially invited.

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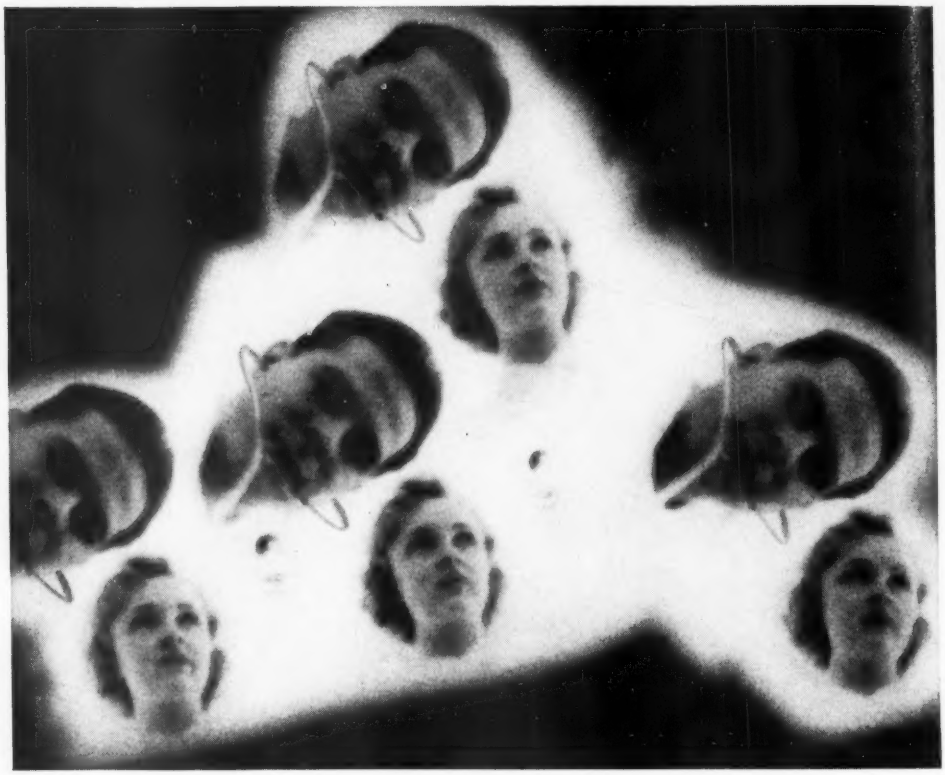

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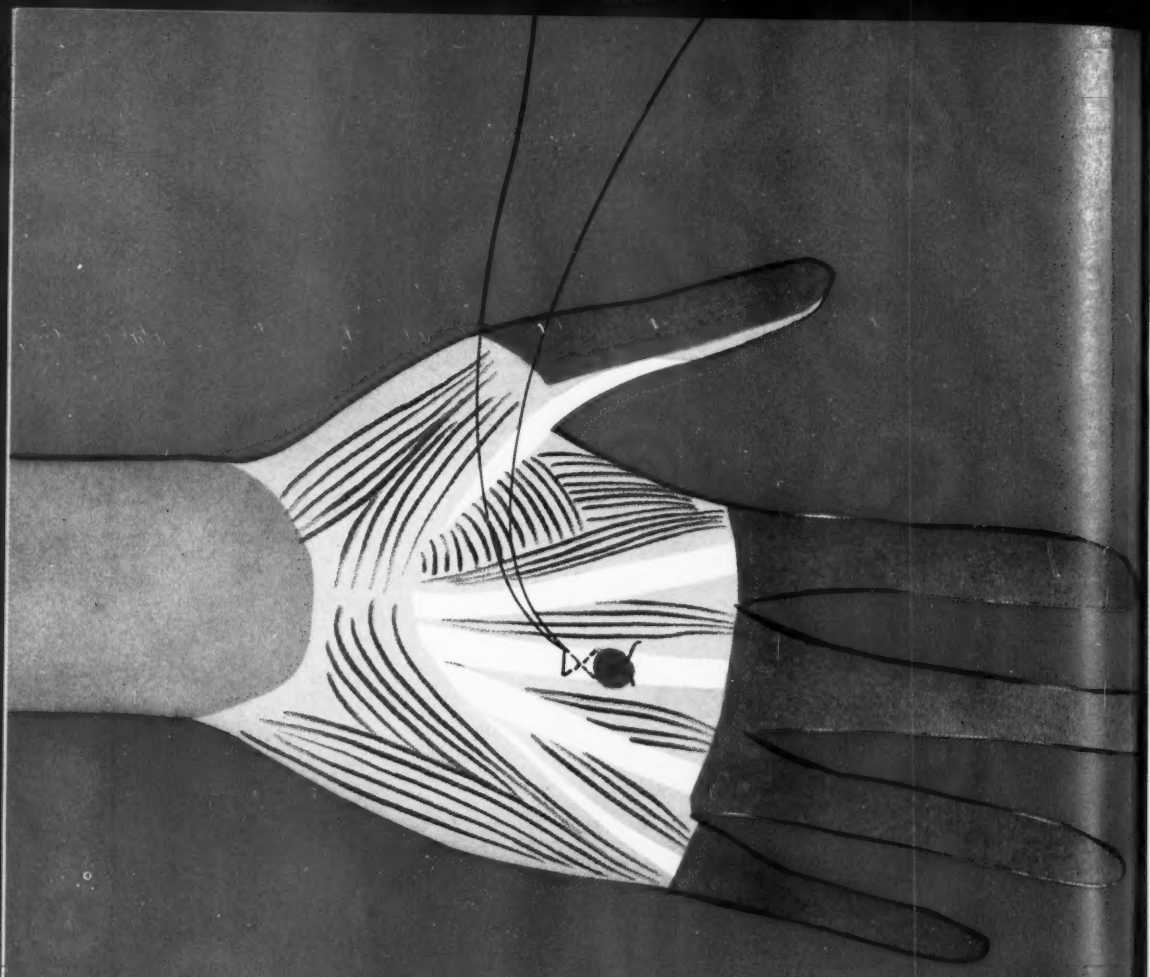

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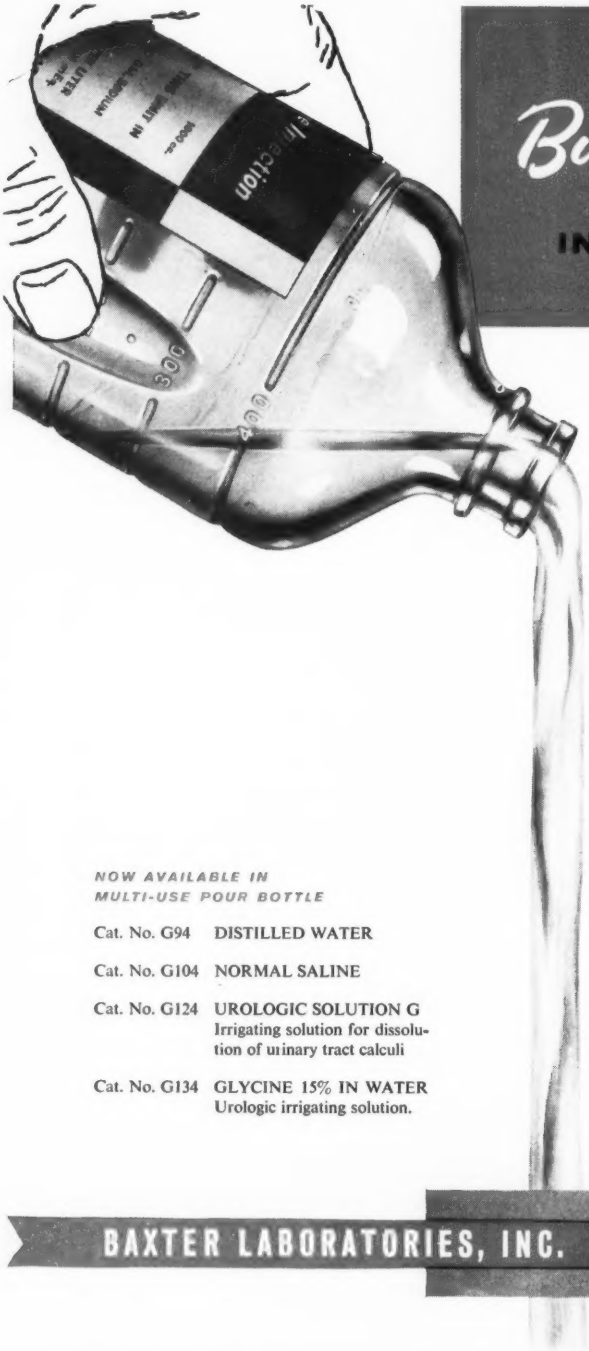

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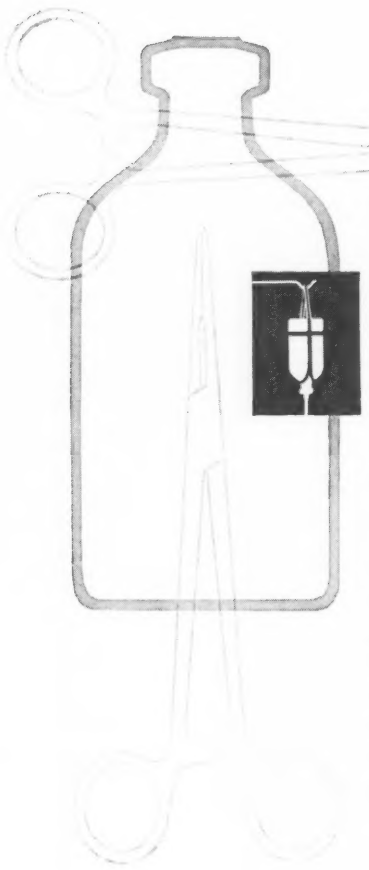

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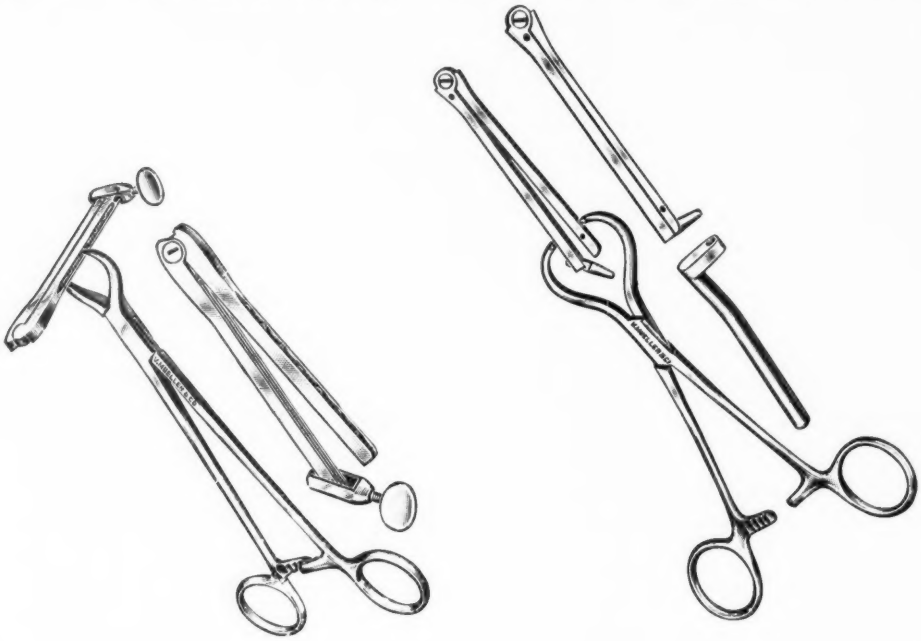

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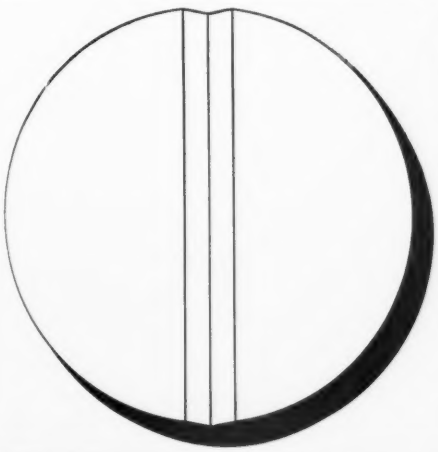

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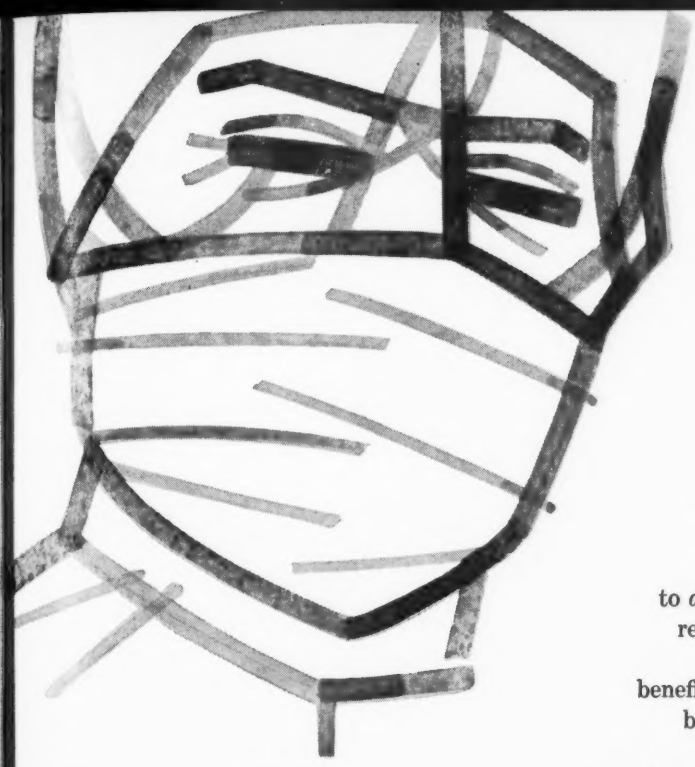

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Relieves tension—mental and muscular

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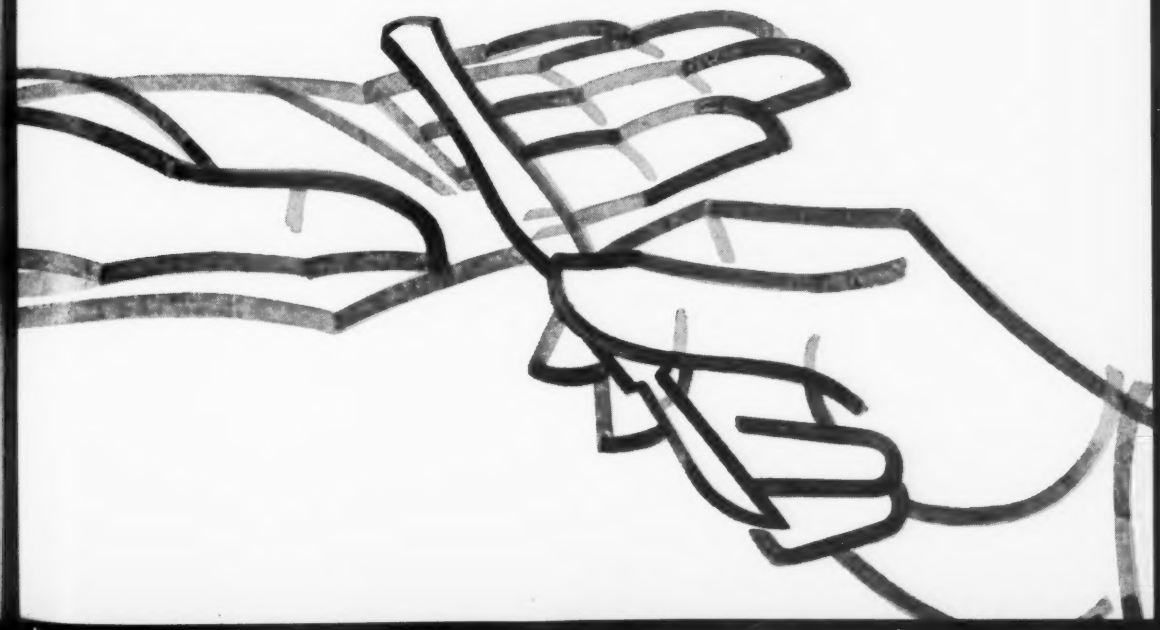

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50 Years of Service to the Surgical Profession

SURGICAL PRODUCTS NEWS

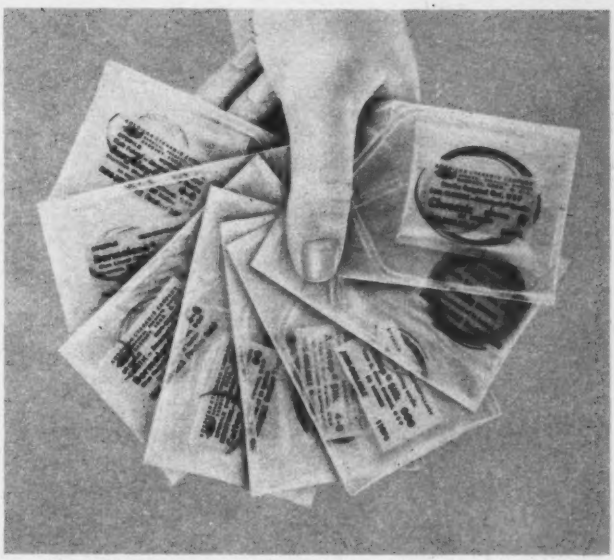
No. 2

SURGEONS MAY NOW SPECIFY SAFER, PLASTIC PACKAGED SUTURES IN A FULL RANGE OF MATERIALS

Complete Line in Individual Double-Envelope Pack Eliminates The Cross-Contamination Hazard of Bulk Storage in Jars and Solutions

Standardization on the complete line of Davis & Geck surgical gut and non-absorbable sutures is proceeding so rapidly in hospitals that Surgical Products Division has stopped all production of sutures in glass tubes!

Hospital administrators, surgeons and operating room supervisors have cited 5 major reasons for their speedy adoption of the new suture line: (1) *Protection against cross-infection.* The individual packaging offers a reassuring safeguard against cross-contamination in common storage jars—particularly against the hepatitis virus which is resistant to *all* known cold germicidal solutions. (2) *Elimination of broken glass.* Both damage to sutures and the risk of infecting personnel through cut gloves and fingers are avoided. (3) *Sutures reach surgeon in better condition.* Opening just before use keeps gut sutures from drying out, and the loose coil which replaces tightly wound reels reduces kinking and excessive handling. (4) *Simplified dispensing.* All three convenient, easily learned dispensing technics have proved important time-savers. (5) *Economy.* Preparing sutures only as needed avoids waste and post-operative sterilization chores. Added savings are achieved by eliminating breakage, preventing damage due to broken glass, and simplifying storage.



Surgilope SP® sutures now include surgical gut, silk, cotton, nylon, polyethylene, and stainless steel—Atraumatic® needles, standard or pre-cut lengths.

FILM AVAILABLE FOR HOSPITAL SHOWINGS

The 20-minute, 16-mm. film on the new Surgilope SP suture dispensing technic—with introduction by Carl Walter, M.D., F.A.C.S.—is available on request. Arrangements may be made through local Surgical Products Division representatives, or by writing direct.

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Far lighter and more porous than standard elasticized bandages, the new elastic bandage helps to speed healing and enhance patient comfort wherever pressure dressings are indicated. Because it clings to itself the bandage is especially easy to apply, and stays neatly in place where other bandages tend to slip or creep. It may be washed and autoclaved without deterioration and is physiologically inert. The new bandage is supplied in 3-yard rolls; 2", 3", 4" and 6" widths are available.

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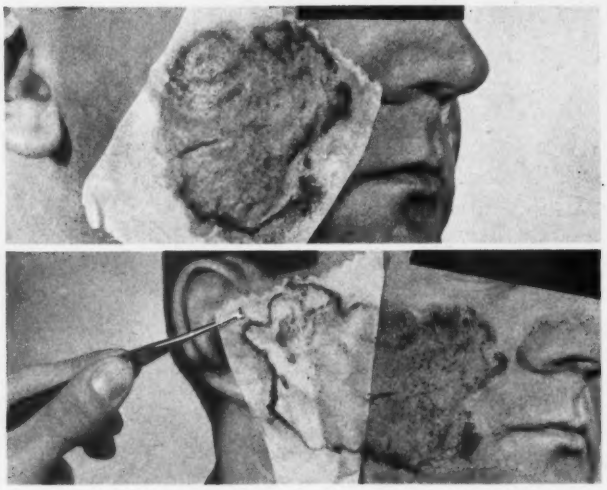

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Packaged sterile in individual envelopes, Owens contact dressings offer a convenient and dependable means of preventing wound adherence on all post-operative sites, surface wounds, burns, granulating areas, and skin graft donor sites. The unique, "micro-gauge" rayon mesh effectively bars capillary penetration without the use of messy occlusive ointments. Liquid exudates pass freely, yet the dressing may be removed without causing unnecessary pain, delaying healing, or impairing cosmetic results. Owens dressings have been used for 4 years in leading hospitals. They are available Plain, or in the new Neomycin-Impregnated form for use on infected or potentially infected wounds. Sizes are 3" x 8" and 8" x 12".

1. Thomson, J. E. M.: Am. J. Surgery 91:413, 1956.

S-2

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Now . . . for the first time, precise positioning and complete immobilization of the skull is possible during even the most rugged neurosurgery whether the patient's position be prone, supine, unilateral or upright.

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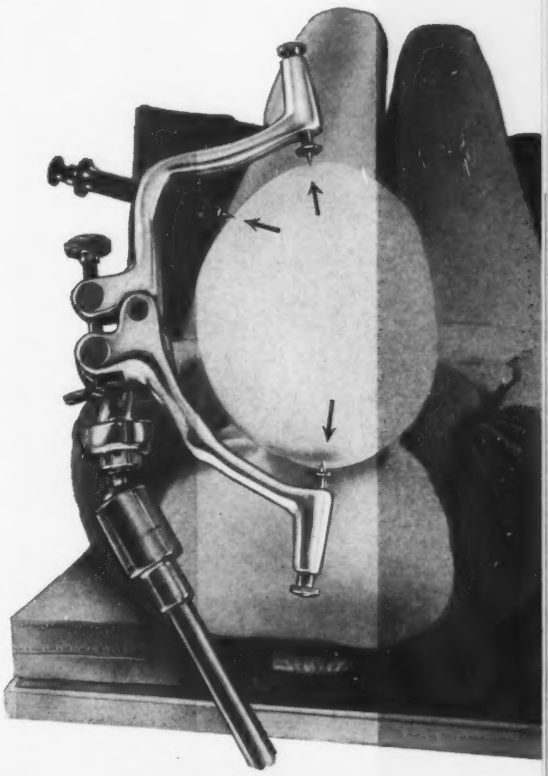

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• Excellent exposure of parietal, occipital and cervical regions.

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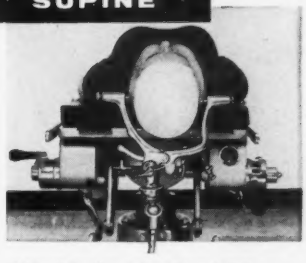

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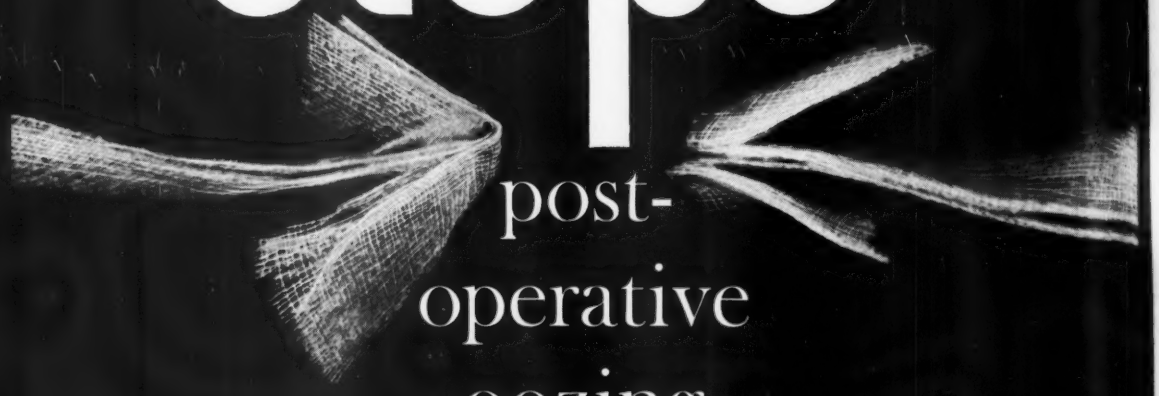

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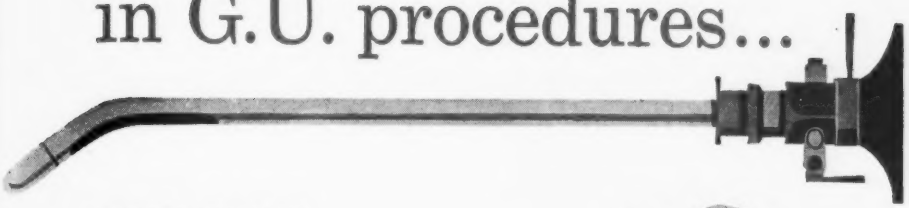

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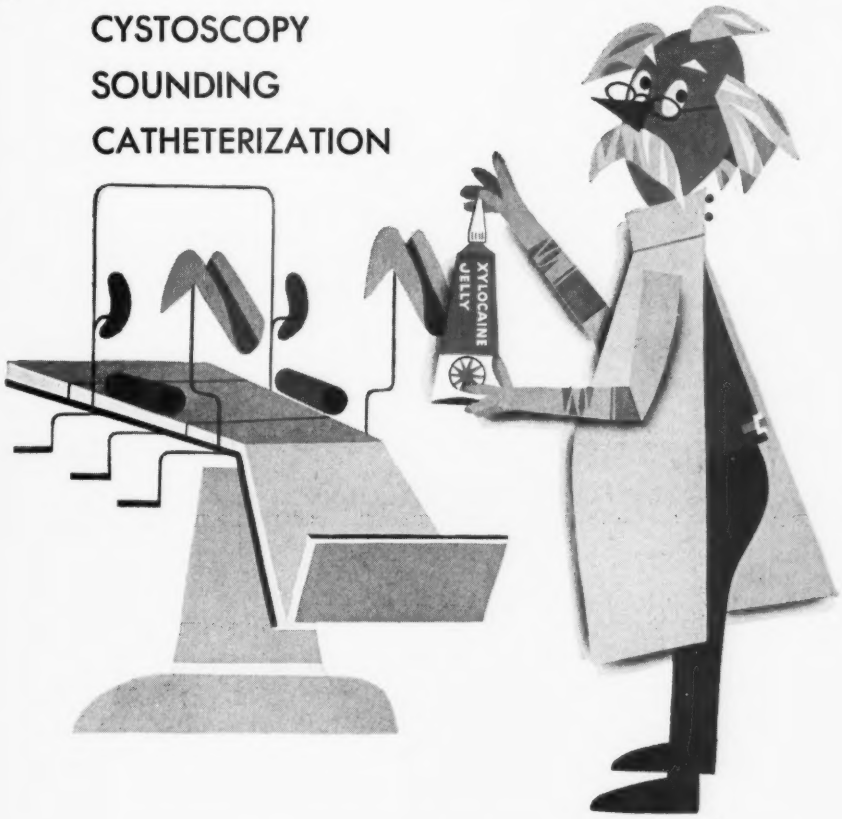

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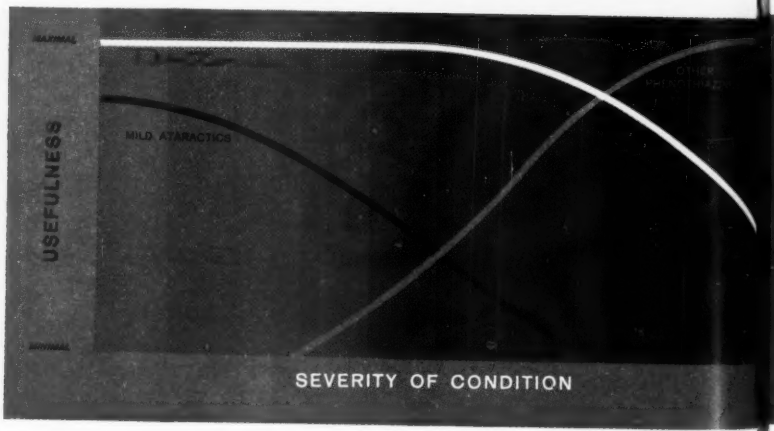

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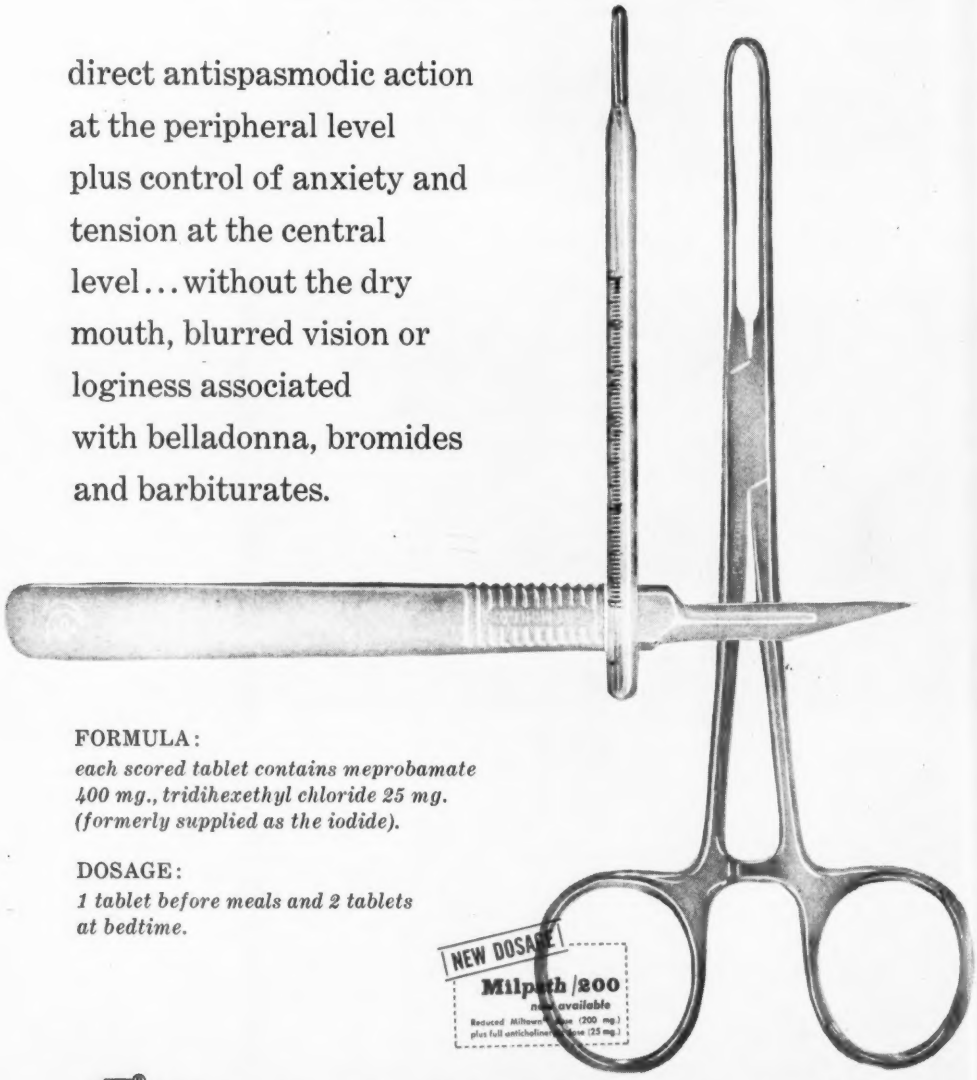

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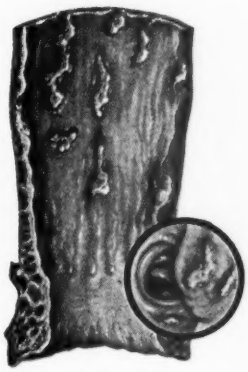

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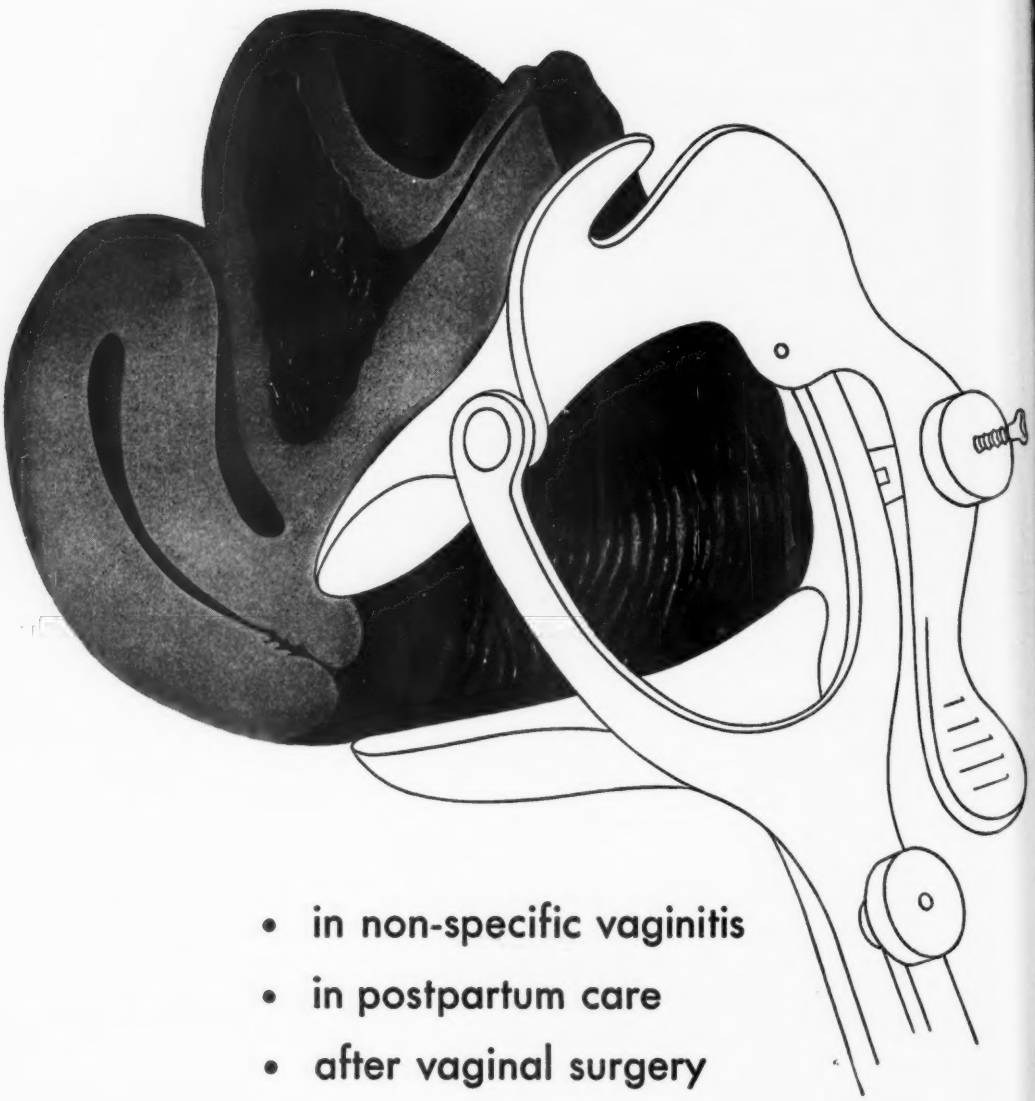

- in non-specific vaginitis
- in postpartum care
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Standard preoperative procedure to control bleeding

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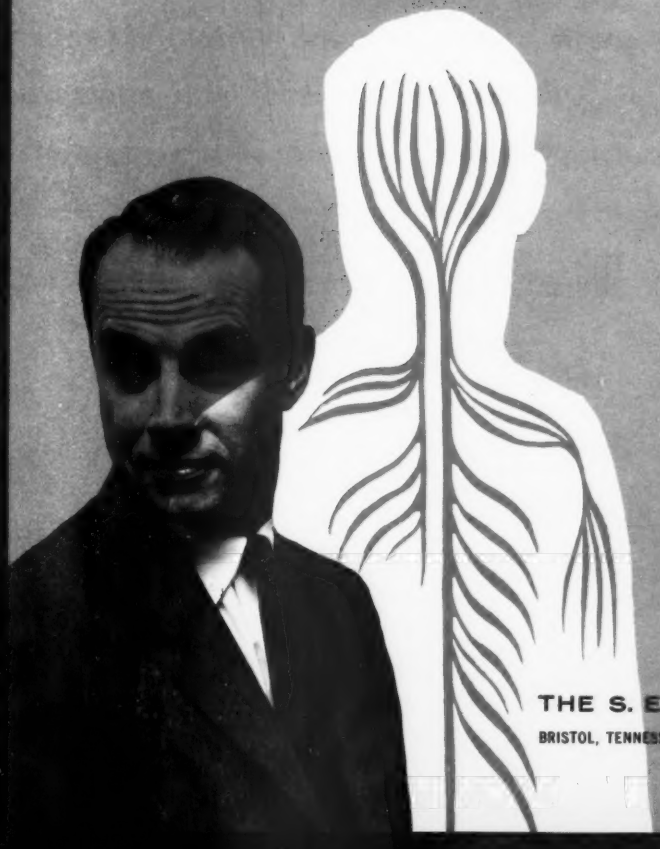

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Adrenosem is recommended preoperatively where bleeding presents a problem. Minimal bleeding provides a clearer operative field and facilitates operative procedures.[9-20,22] Postoperatively, it lessens the need for transfused blood.[2,6,9-11,13,15,18,20,22]

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Adrenosem is an effective hemostatic where vascular anomalies exist, such as telangiectasia, purpuras, epistaxis, and others.[1-4,6,9-11,27-29] At recommended dosage levels there are no contraindications.

Supplied: Ampuls, 1 cc., 5 mg.; Tablets, 1 and 2.5 mg.; Syrup, each 5 cc., 2.5 mg. Potency of all dosage forms is stated in terms of the active ingredient, adrenochrome monosemicarbazone.

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rrhaphy *pericardiorrhaphy* **splenectomy** *stomatoplasty* **cheiloplasty** *uvulectomy*

ity **esophagectomy** *gastrectomy* **enterotomy** *proctectomy* **proctopexy** *sphincter*

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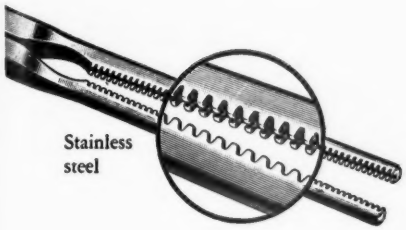

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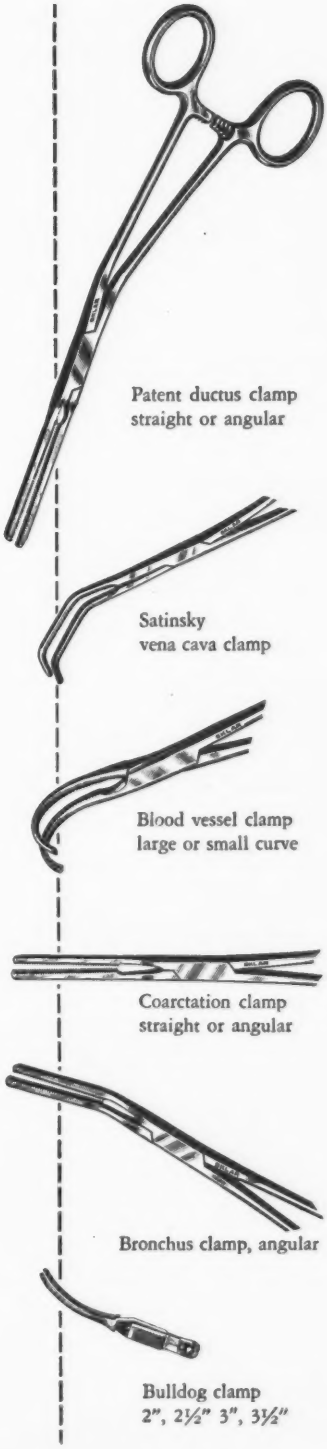

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straight or angular

Satinsky
vena cava clamp

Blood vessel clamp
large or small curve

Coarctation clamp
straight or angular

Bronchus clamp, angular

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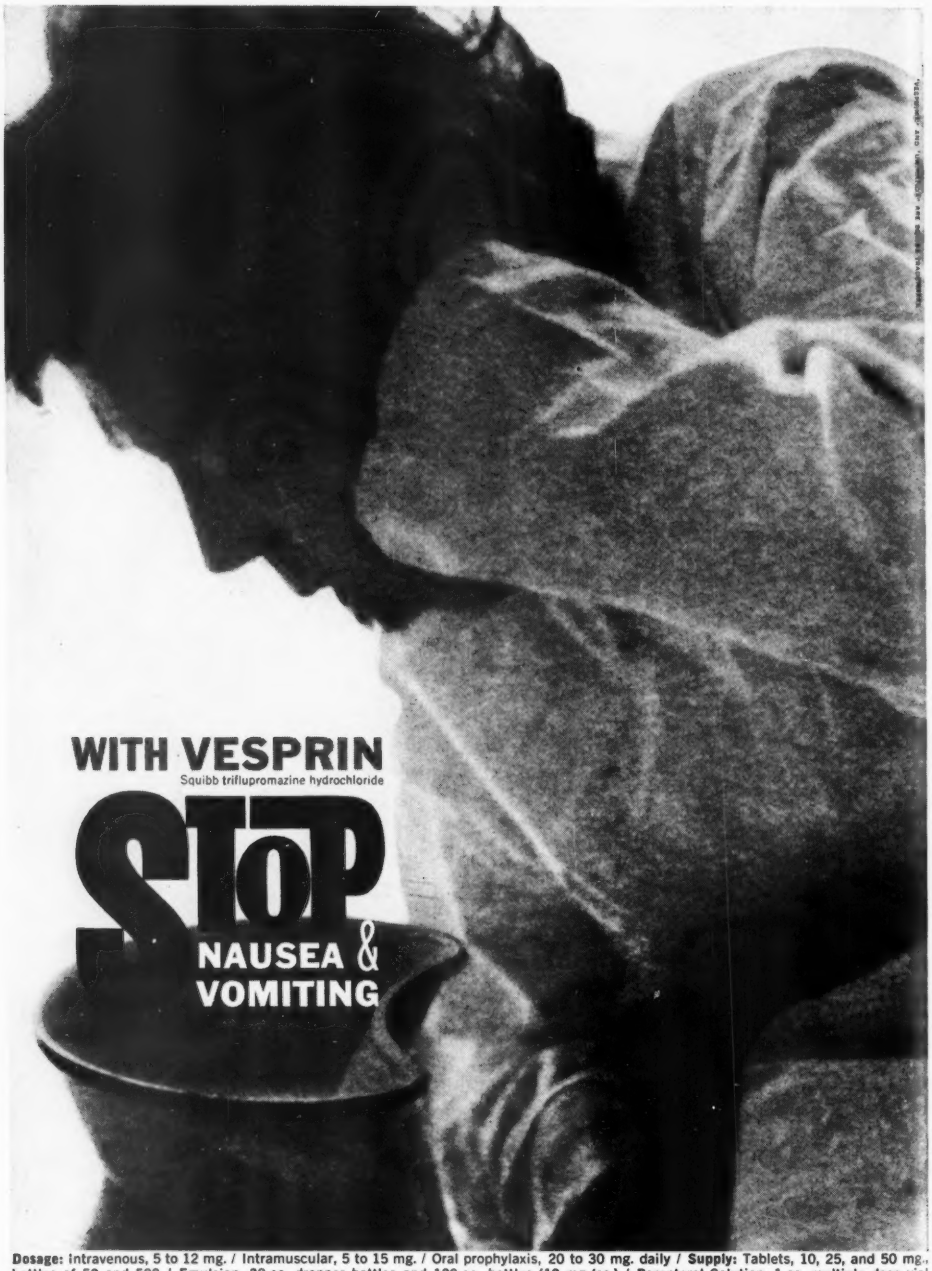
2", 2½" 3", 3½"



Dosage: Intravenous, 5 to 12 mg. / Intramuscular, 5 to 15 mg. / Oral prophylaxis, 20 to 30 mg. daily / **Supply:** Tablets, 10, 25, and 50 mg., bottles of 50 and 500 / Emulsion, 30-cc. dropper bottles and 120-cc. bottles (10 mg./cc.) / Parenteral Solution, 1-cc. multiple dose vial (20 mg./cc.) / 10-cc. multiple dose vial (10 mg./cc.) / Vesprin Injection Unimatic (15 mg. in 0.75 cc.)

Vesprin/the tranquilizer that fills a need in every major area of medical practice/ anxiety and tension states, pre- and postoperative tranquilization, alcoholism, and obstetrics

SQUIBB

Squibb Quality – the Priceless Ingredient

faster recovery, greater comfort for your OB-GYN patients

Administered before and after cervicovaginal surgery, irradiation, delivery, and office procedures such as cauterization, FURACIN CREAM promptly controls infection; reduces discharge, irritation and malodor; hastens healing. FURACIN CREAM is active in the presence of exudates, yet is nontoxic to regenerating tissue, does not induce significant bacterial resistance nor encourage monilial overgrowth.

FURACIN® CREAM

BRAND OF NITROFURAZONE

FURACIN 0.2% in a fine cream base, water-miscible and self-emulsifying in body fluids. Tubes of 3 oz., with plastic plunger-type vaginal applicator. Also available: FURACIN Vaginal Suppositories.

THE NITROFURANS—a *unique* class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK

in surgical and obstetrical procedures
where apprehension increases tension...
patients respond well to

VISTARIL®

hydroxyzine pamoate

EFFECTIVENESS AND SAFETY Vistaril establishes relaxed indifference to preoperative preparation without serious hypotensive effects.

PSYCHOTHERAPEUTIC POTENCY Vistaril makes possible the maintenance of an adequate degree of narcosis with reduced doses of narcotics.
Vistaril relieves tension and controls emesis in both postoperative and postpartum patients.

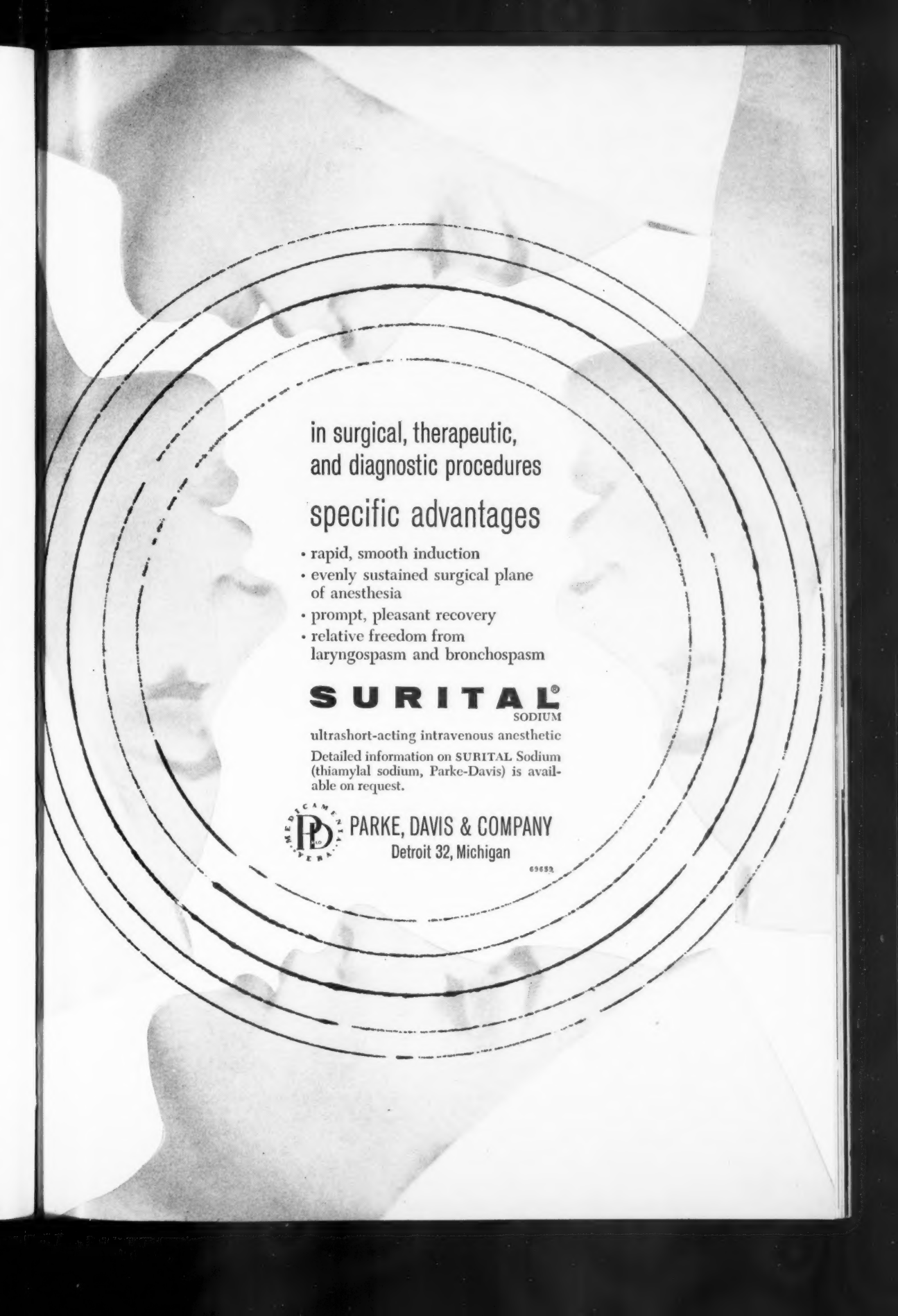
Recommended Oral Dosage: up to 400 mg. daily in divided doses.

Recommended Parenteral Dosage: 25-50 mg. (1-2 cc.) I. M., q. 4 h., p.r.n.

Vistaril is supplied in 25 mg., 50 mg., and 100 mg. capsules. The parenteral solution is available in 10-cc. vials and 2-cc. Steraject® cartridges; each cc. contains 25 mg. hydroxyzine (as the HCl).

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, New York


in surgical, therapeutic,
and diagnostic procedures
specific advantages
• rapid, smooth induction
• evenly sustained surgical plane of anesthesia
• prompt, pleasant recovery
• relative freedom from laryngospasm and bronchospasm
SURITAL®
SODIUM
ultrashort-acting intravenous anesthetic
Detailed information on SURITAL Sodium (thiamylal sodium, Parke-Davis) is available on request.
PARKE, DAVIS & COMPANY
Detroit 32, Michigan
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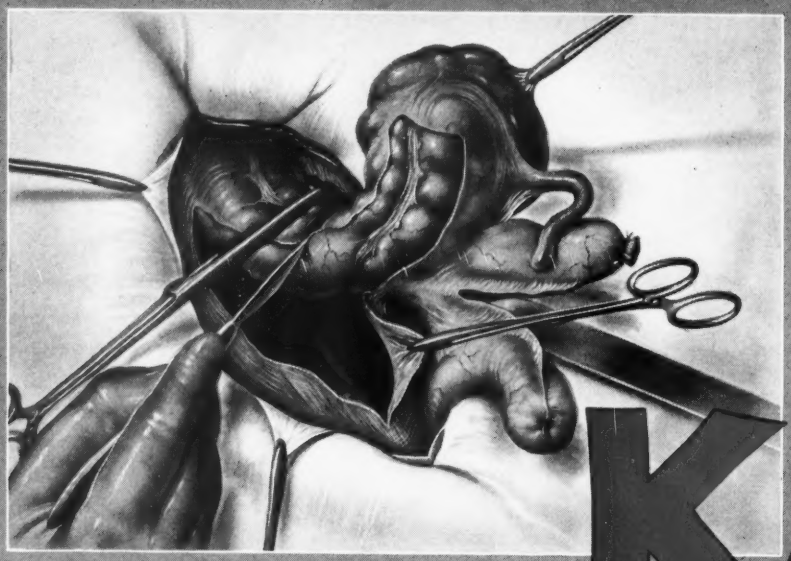
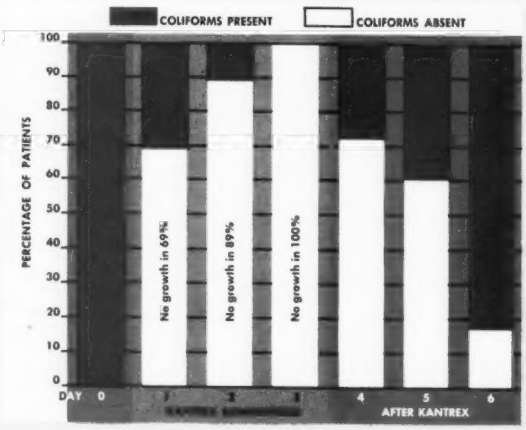
For preoperati



KA

COLIFORMS REMOVED FROM STOOLS OF MAJORITY OF PATIENTS AFTER ONE DAY OF KANTREX THERAPY[1]



In this study, coliforms were found in all 18 control specimens before KANTREX was administered. By the end of the first day of therapy, they had been removed from 69% of the patients; by the end of the second day, from 89% of the patients; and by the end of the third day, from all of the patients. Following cessation of therapy, the intestinal microflora returned rapidly to normal. KANTREX dosage consisted of 1 Gm. (2 capsules) every hour for 4 hours, then 1 Gm. every 6 hours for 72 hours

bowel sterilization–

"the only single agent" to be recommended out of 30 drugs, combinations and dosages studied[1]...

KANTREX®

KANAMYCIN SULFATE

CAPSULES

FOR ORAL USE ONLY
Not for systemic infections

Based on experience with "more than 30 drugs, drug combinations, and drug dosages" for bowel sterilization, Cohn reported that KANTREX is "the only *single* agent" that can be recommended for such use, and is "superior to neomycin."[1] In another report, Cohn and Longacre cited the advantages of KANTREX as: negligible absorption from the gastrointestinal tract, "rapid and satisfactory control of streptococci, coliforms, and clostridia," and the failure of yeasts or staphylococci to proliferate during therapy.[2] Still others have termed it "an excellent intestinal antiseptic."[3]

DOSAGE FOR PREOPERATIVE BOWEL STERILIZATION: 1.0 Gm. (2 capsules) every hour for 4 hours, followed by 1.0 Gm. (2 capsules) every 6 hours for 36 to 72 hours. Duration of therapy depends on condition of patient, concurrent mechanical cleansing, and clinical judgment of the surgeon.

KANTREX Capsules are also indicated in the treatment of intestinal infections due to kanamycin-sensitive organisms, including Shigella and Salmonella.

Supply: KANTREX (kanamycin sulfate) Capsules, 0.5 Gm., in bottles of 20 and 100.

References: 1. Cohn, I., Jr.: Annals N. Y. Acad. Sci. 76:212, 1958. 2. Cohn, I., Jr., and Longacre, A. B.: S. G. & O. 108:100, 1959. 3. Finegold, S. M., *et al.*: Annals N. Y. Acad. Sci. 76:319, 1958.

KANTREX Sensitivity Discs and comprehensive literature available on request.

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BRISTOL LABORATORIES INC., SYRACUSE, N.Y.

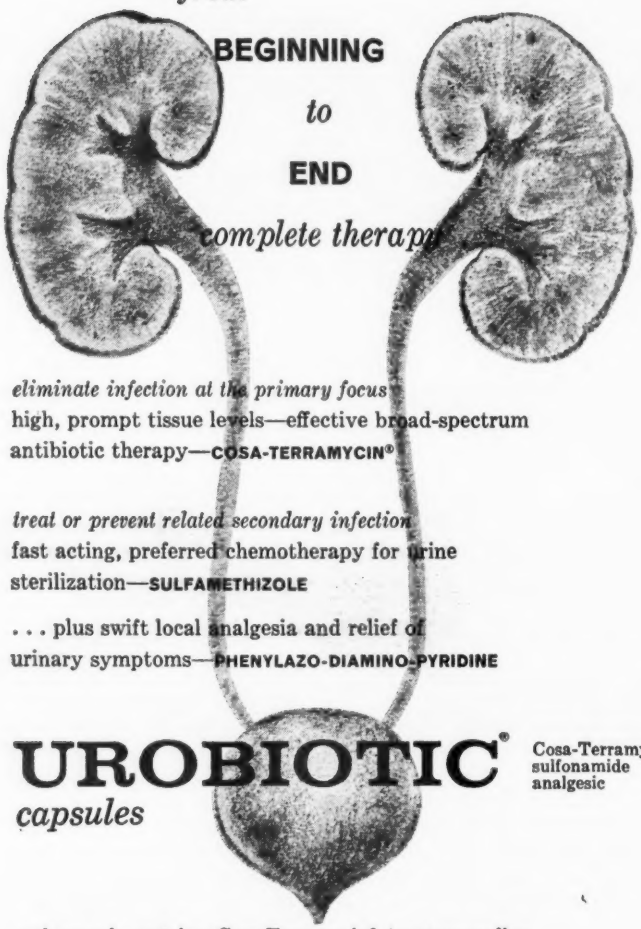
from

BEGINNING

to

END

complete therapy



eliminate infection at the primary focus
high, prompt tissue levels—effective broad-spectrum antibiotic therapy—**COSA-TERRAMYCIN®**

treat or prevent related secondary infection
fast acting, preferred chemotherapy for urine sterilization—**SULFAMETHIZOLE**

. . . plus swift local analgesia and relief of urinary symptoms—**PHENYLAZO-DIAMINO-PYRIDINE**

UROBIOTIC®
capsules

Cosa-Terramycin®
sulfonamide
analgesic

each capsule contains: Cosa-Terramycin® (oxytetracycline with glucosamine) 125 mg.; sulfamethizole 250 mg.; phenylazo-diamino-pyridine HCl 50 mg.
dosage: 1 to 2 capsules four times daily.

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POROUS TAPES

PERMIT THE SKIN

TO "BREATHE"

POROUS

Available Now in
1″, 2″, 3″ and 4″ widths

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ZONAS TAPE TOO IS POROUS!

Now, a new J&J process imparts the same *porous* feature to ZONAS "regular" (non-elastic) adhesive tape.

A unique method of coating creates hundreds of porelike holes in the adhesive mass which allow perspiration to escape from the skin.

Because it too, permits the skin to "breathe", ZONAS *porous* tape minimizes a significant cause of irritation and is more comfortable for the patient.

ZONAS® Porous Adhesive Tape

NOW AVAILABLE in 12" x 10 yd. rack rolls in the following widths:
½", 1", 1½", 2", 3", 4" and assorted.

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HELPING THE HANDS THAT HEAL

Announcing

PROZINE*

meprobamate and promazine hydrochloride, Wyeth

SPECIFIC CONTROL OF EMOTIONAL DISTURBANCES THROUGH DUAL ACTION

PROZINE controls anxiety and tension as well as motor excitability. This effect on the components of emotional reaction is possible because of the dual sites of action of PROZINE—the thalamic and hypothalamic areas of the brain. The unique dual action of PROZINE enables the physician to exert more specific control over emotionally disturbed patients.

PROZINE controls emotional disturbances manifested by apprehension and agitation, insomnia, nausea and vomiting, gastrointestinal symptoms, alcoholism, menopausal symptoms, premenstrual tension.

PROZINE is indicated in patients having a primary emotional disturbance, in patients having an emotional disturbance unrelated to their organic disease, and in patients emotionally disturbed by primary organic disease. PROZINE is especially useful in overly apprehensive medical patients—including surgical and obstetrical—and in emotional problems of children, adolescents, and the aged. It also is useful in emotionally disturbed patients who receive little or no relief from analgesics, barbiturates, anticholinergics, antihypertensives, and hormones (estrogens and corticoids).

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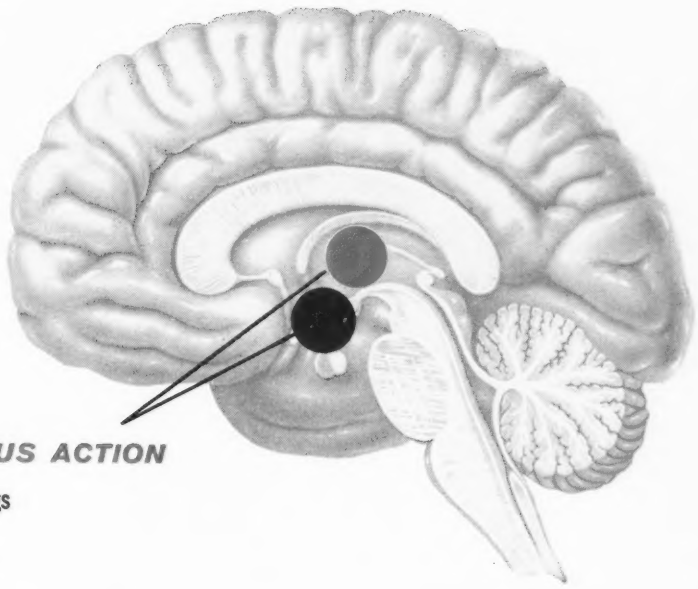

SIMULTANEOUS ACTION

of two psychotropic drugs
affecting two areas
of the brain, produces
more **SPECIFIC CONTROL**

PROZINE in the recommended dosage (1 or 2 capsules, 3 or 4 times daily) produces more specific control than is obtainable with high doses of other ataractic agents.

thus— ***in emotionally disturbed patients*** on **PROZINE** the dose required is diminished to the point where the incidence of side-effects and toxicity reactions is minimal* and the patient is calm, tranquil, and amenable to additional therapy, whether it be educational, medical, or psychiatric.

Supplied: Bottles of 50 capsules, each containing 200 mg. of meprobamate and 25 mg. of promazine hydrochloride.
Comprehensive literature available

Wyeth
Philadelphia 1, Pa.

*In studies involving 972 patients suffering a variety of emotional diseases, related and unrelated to physical ailments, 78 per cent were improved; the incidence of side-effects was only 3.7 per cent.

for those post-op sounds you want to hear - - earlier, safely!

ILOPAN®

(d-Pantothenyl Alcohol, Warren-Teed)

Clinical studies and hundreds of individual case histories, convincingly attest the effectiveness of ILOPAN against postoperative intestinal distention — even paralytic ileus. Surgical stress appears to increase pantothenic acid requirements. Ilopan provides additional pantothenic acid to restore normal peristalsis — often dramatically. ILOPAN is safe — can be routinely administered intramuscularly by the nurse — can't produce more than normal peristalsis — isn't contraindicated even under conditions of mechanical bowel obstructions.

Supplied in:

2 cc. AMPULS
(500 mg.)

10 cc. VIALS
(250 mg. per cc.)

THE WARREN-TEED PRODUCTS COMPANY
COLUMBUS 8, OHIO

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WARREN-TEED PHARMACEUTICALS

which antibiotic should I use first?

in skin, soft tissue and post-surgical infections–
in genito-urinary infections–
in respiratory tract infections–

due to staph or "gram negatives"

a
"first choice"
antibiotic
to use
is

KANTREX

because... (see over)

Kantrex is a first choice antibiotic for use in infections due to staph and "gram negatives"...

because it is:

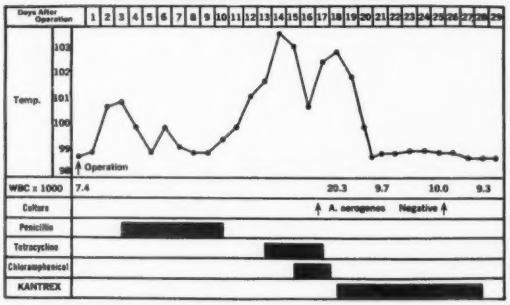
- bactericidal—not merely bacteriostatic
- rapid-acting
- effective against a wide range of organisms, including many strains resistant to other antibiotics
- clinically safe in specified dosage
- less likely to lead to the development of resistant organisms in clinical usage
- "most likely to succeed"—in saving time, cutting the cost of illness, reducing complications and bringing about a successful therapeutic result

because it is: clinically proven

in over 1000 cases by 111 investigators, reported in 42 published papers

POST-SURGICAL INFECTION
KANTREX Clinical Report No. 799

RAPID RESPONSE TO KANTREX



E. D., a 73-year-old male, underwent a suprapubic cystotomy and fulguration of papillary carcinoma of the bladder. His temperature began rising on the 10th postoperative day; subsequently urine and blood cultures yielded *A. aerogenes*. After penicillin, tetracycline and chloramphenicol failed to alter the course of the infection, KANTREX brought about a dramatically improvement.

— Rutenburg, A. M., et al.: Annals N.Y. Acad. Sci. 76:348, 1958.

typical dramatic response

(even after other antibiotics failed)

Supply: Available as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in 2 ml. volume.

KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in 3 ml. volume.

KANTREX® INJECTION

KANTREX Sensitivity Discs and comprehensive literature available on request

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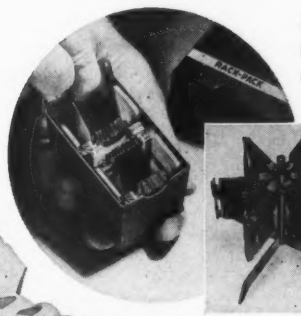
An EDGE on them all

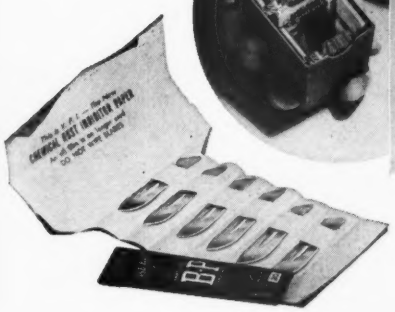
.Cutting efficiency and maximum blade performance has always been the surgeon's first consideration when choosing a surgical blade. BARD-PARKER offers you a blade made with the same consideration in mind . . . a blade of *carbon steel* of course . . . so superior for *fine cutting edges*.

B-P RIB-BACK Blades are now available . . .



in the Puncture Proof Sterile Blade package that can be autoclaved.

in the RACK-PACK package—blades pre-racked ready for sterilization.



in the CONVENTIONAL package—six of one size in a rust-proof wrapper.

It's Sharp

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DERMOPLAST®

AEROSOL SPRAY

SOOTHING TOPICAL ANESTHETIC • BACTERICIDAL • FUNGICIDAL

APPLIED WITHOUT TOUCHING THE INVOLVED SENSITIVE AREAS—*Immediate relief of pain and itching is experienced*

Formula: benzocaine 4.7% benzethonium chloride 0.1%; menthol 0.5%; dissolved in oils (DOHO PROCESS)

Available in 3 sizes:

PRESCRIPTION: new 3 oz. (for individual therapy in hospital & home)

HOSPITAL: 12 oz. economy

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Other indications responding to DERMOPLAST's quick, therapeutic pain relief:

perineal suturing
hemorrhoids
pruritus vulvae
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Supporting clinical data on request

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New Aristocort®

Triamcinolone Diacetate LEDERLE

Parenteral

for
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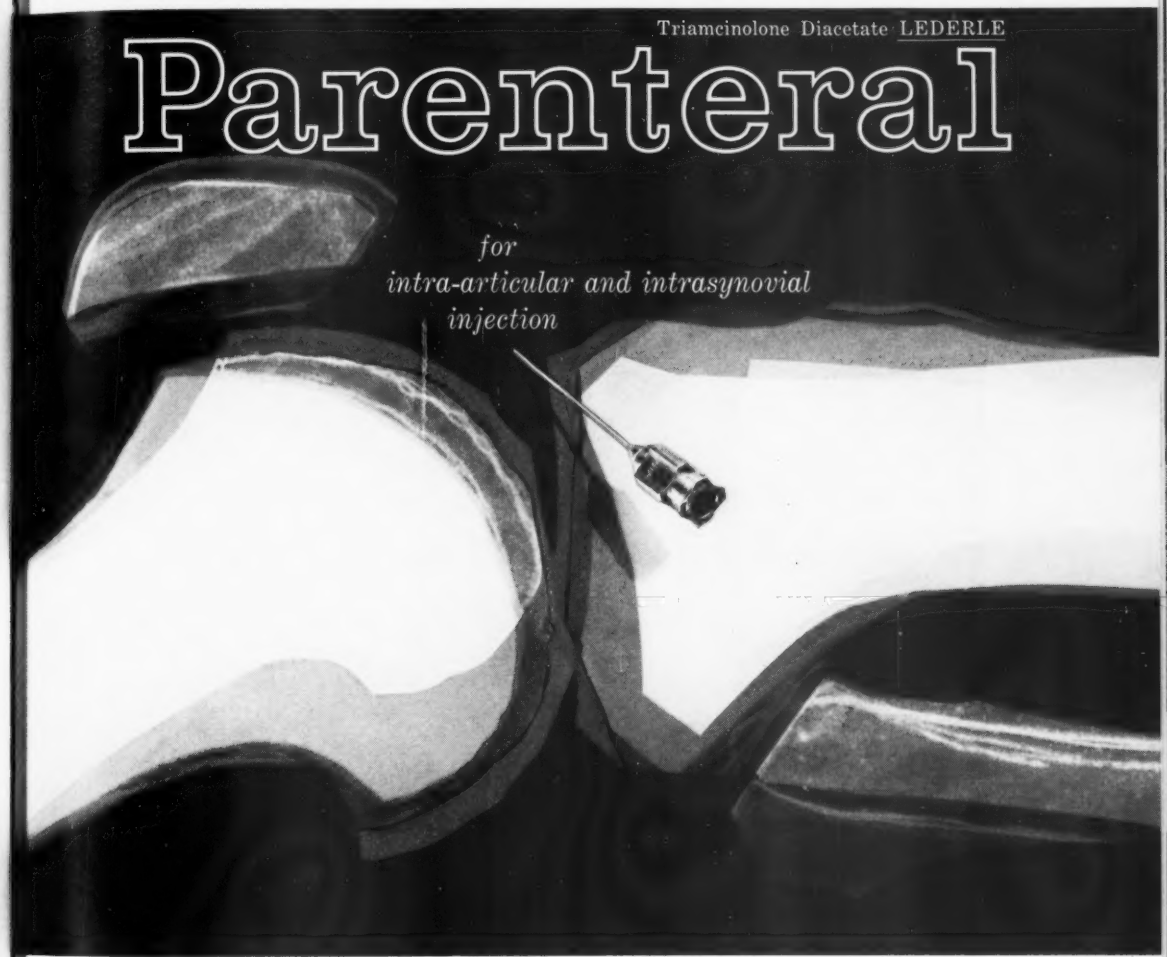
injection



longer and *more pronounced* anti-inflammatory action in the *shortest time*

When systemic therapy is contraindicated • when systemic corticosteroids produce serious side effects
To secure quick relief in one or two joints • for use in conjunction with orthopedic procedures

Indications: rheumatoid arthritis; osteoarthritis; bursitis; peritendinitis; ganglion; intermittent hydroarthrosis; epicondylitis and related conditions.

ARISTOCORT Parenteral contains: 25 mg. per cc. of ARISTOCORT® Triamcinolone Diacetate micronized; polysorbate 80 U.S.P. 0.10%; benzyl alcohol 0.95%; benzalkonium chloride 0.01%; sorbitol solution N.F. 84.83%, and water for injection q.s. 100%.

All precautions required for intra-articular and intrasynovial administration of other corticosteroids should also be observed with ARISTOCORT Parenteral.

Complete information on dosage and administration is included in the package circular.

Supply: Vials of 5 cc. (25 mg. per cc.)

Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

rapid onset–prolonged duration in all local anesthetic procedures

CYCLAINE® Hydrochloride

(HEXYLCAINE HYDROCHLORIDE)

SURFACE ANESTHESIA "CYCLAINE combines a greater spectrum of useful local anesthetic activity with a greater margin of safety. It is as active for surface anesthesia as for block and infiltration anesthesia."[1] Supplied as 5% topical solution and 5% jelly.

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references: 1. Current Researches in Anesth. & Analges. 33:275, July-August 1954. 2. J. Urol. 72:266, August 1954. 3. Anesthesiology 16:386, May 1955. 4. Western J. Surg., Gynec. & Obst. 59:533, October 1951.

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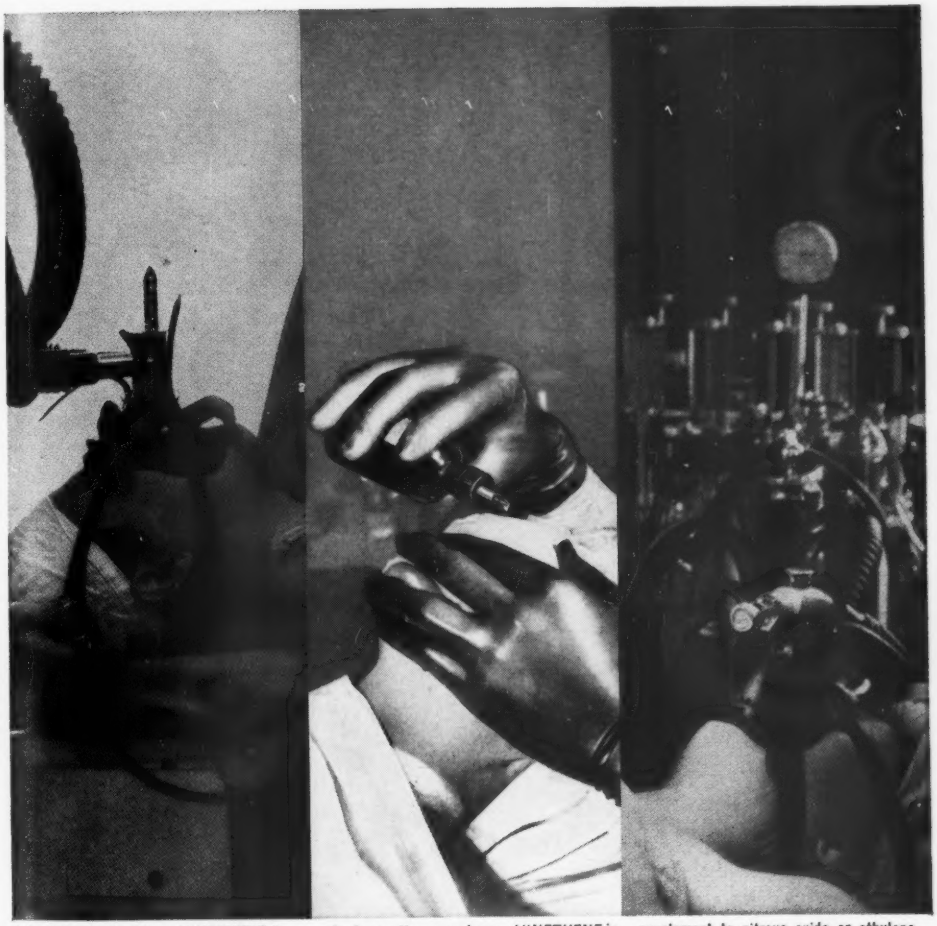
for anesthesia in quietness and confidence

VINETHENE®

VINYL ETHER FOR ANESTHESIA, U.S.P.



induction prior to ether—VINETHENE "... is more rapid and smooth than nitrous oxide and the excitement period is practically eliminated."[1] May be administered with closed technic.

short operative procedures—VINETHENE is easily administered by open-drop method. Induction and recovery are pleasant and rapid, muscular relaxation is good, and excitement or nausea is rarely observed.

supplement to nitrous oxide or ethylene—VINETHENE with ethylene-oxygen or nitrous oxide-oxygen complements these drugs and permits utilization of more oxygen. Ideal for brief surgical procedures.

1. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, The Macmillan Company, 1955, p. 69.

supplied: In 10-cc., 25-cc., 50-cc., and 75-cc. bottles, each with adjustable plastic dropper cap.

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rapid onset–prolonged duration in all local anesthetic procedures

CYCLAINE® Hydrochloride

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SURFACE ANESTHESIA "CYCLAINE combines a greater spectrum of useful local anesthetic activity with a greater margin of safety. It is as active for surface anesthesia as for block and infiltration anesthesia."[1] Supplied as 5% topical solution and 5% jelly.

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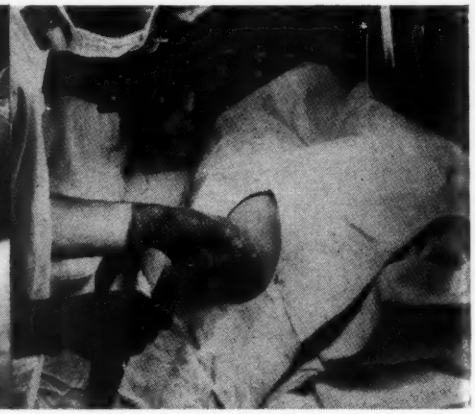

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induction prior to ether—VINETHENE "... is more rapid and smooth than nitrous oxide and the excitement period is practically eliminated."[1] May be administered with closed technic.

short operative procedures—VINETHENE is easily administered by open-drop method. Induction and recovery are pleasant and rapid, muscular relaxation is good, and excitement or nausea is rarely observed.

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- *Prompt remission of symptoms*
- *Bleeding and frequency of stools sharply reduced*
- *Healing of rectal mucosa within a month in most cases*
- *Can be given safely over long periods of time*

Azulfidine®

BRAND OF SALICYLAZOSULFAPYRIDINE

the most valuable drug in the treatment of

Ulcerative Colitis

"The most widely accepted sulfonamide preparation today for the therapy of chronic ulcerative colitis is salicylazosulfapyridine (Azulfidine)."

Hightower, N.C., Jr., and others:
Am. J. Digest. Dis.: 3:931 (Dec.) 1958

Also valuable in treatment of regional enteritis and other forms of colitis

Pharmacia Laboratories, Inc.
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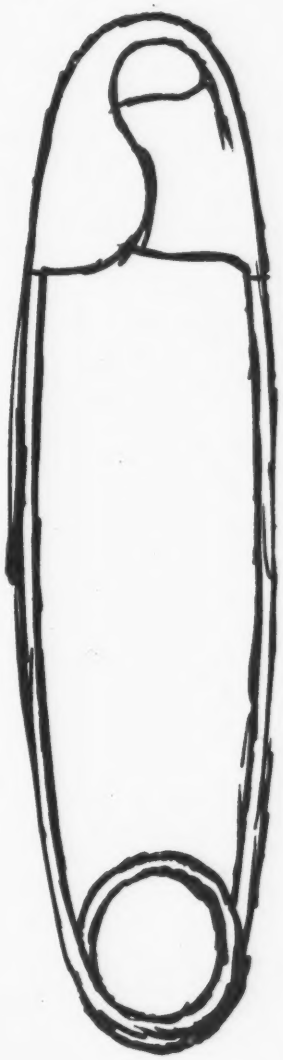
NUGESTORAL®

in the treatment of habitual abortion



NUGESTORAL will help you bring the abortion-prone patient to term by supplying five agents known to contribute to fetal salvage. It creates an optimal environment for the maintenance of pregnancy.

CLINICAL REPORT

Fitzgerald* has reported a fetal salvage rate of 50% in a group of habitual aborters with the addition of NUGESTORAL to his standard regimen for abortion-prone patients.

*Fitzgerald, W.: Clinical Medicine, 5:1037, 1958.

Formula: A daily dose of three NUGESTORAL tablets provides 45 mg. Progestoral® (Ethisterone); 525 mg. Ascorbic Acid; 525 mg. Hesperidin; 6 mg. Sodium Menadiol Diphosphate (Vit. K Analogue); 10.5 mg. dl, Alpha-Tocopherol Acetate (Vit. E).

Issued: For greater patient economy NUGESTORAL is now available in boxes of 100 gold foil wrapped tablets as well as in boxes of 30.

Organon Inc.

ORANGE, NEW JERSEY

Eradicate Infection and Restore Normal Vaginal Flora...

New-'Neosporin'® brand Vaginal Suppositories

Trichomonacidal · Bactericidal

Each suppository contains:

'Aerosporin'® brand Polymyxin B Sulfate	20,000 Units
Neomycin Sulfate	5 mg.
Acetarsone	250 mg.
Beta-lactose	q.s. (approx. 1 Gm.)

In a base containing a surface active agent
Foil-wrapped—Box of 12

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your obese patient needs individualized therapy

The emotional and social pressures which intensify overeating problems may vary considerably in your obese patients. Therapeutically sound individualization of antiobesity regimens is thus not only desirable, but also simply achieved with the different forms of Ambar.

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(PARABROMDYLAMINE MALEATE)

Dimetane® works!

NOW

. . . a new way to relieve pain and stiffness in muscles and joints

INDICATED IN:

MUSCLE STIFFNESS

LUMBOSACRAL STRAIN

SACROILIAC STRAIN

WHIPLASH INJURY

BURSITIS

SPRAINS

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FIBROSITIS

FIBROMYOSITIS

LOW BACK PAIN

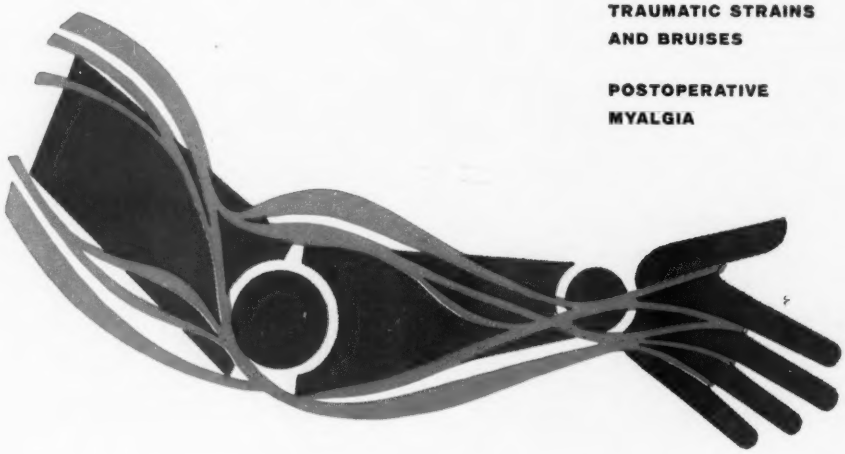
DISC SYNDROME

SPRAINED BACK

"TIGHT NECK"

TRAUMATIC STRAINS AND BRUISES

POSTOPERATIVE MYALGIA



■ Exhibits unusual analgesic properties, different from those of any other drug ■ Specific and superior in relief of SOMAtic pain ■ Modifies central perception of pain without abolishing natural defense reflexes ■ Relaxes abnormal tension of skeletal muscle

SOMA™

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

■ More specific than salicylates ■ Less drastic than steroids

■ More effective than muscle relaxants

SOMA has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. SOMA is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with SOMA than with any previously used analgesic, sedative or relaxant drug.
SOMA also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

ACTS FAST. Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

NOTABLY SAFE. Toxicity of SOMA is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy on high dosage.

EASY TO USE. Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

SUPPLIED: Bottles of 50 white sugar-coated 350 mg. tablets.
Literature and samples on request.

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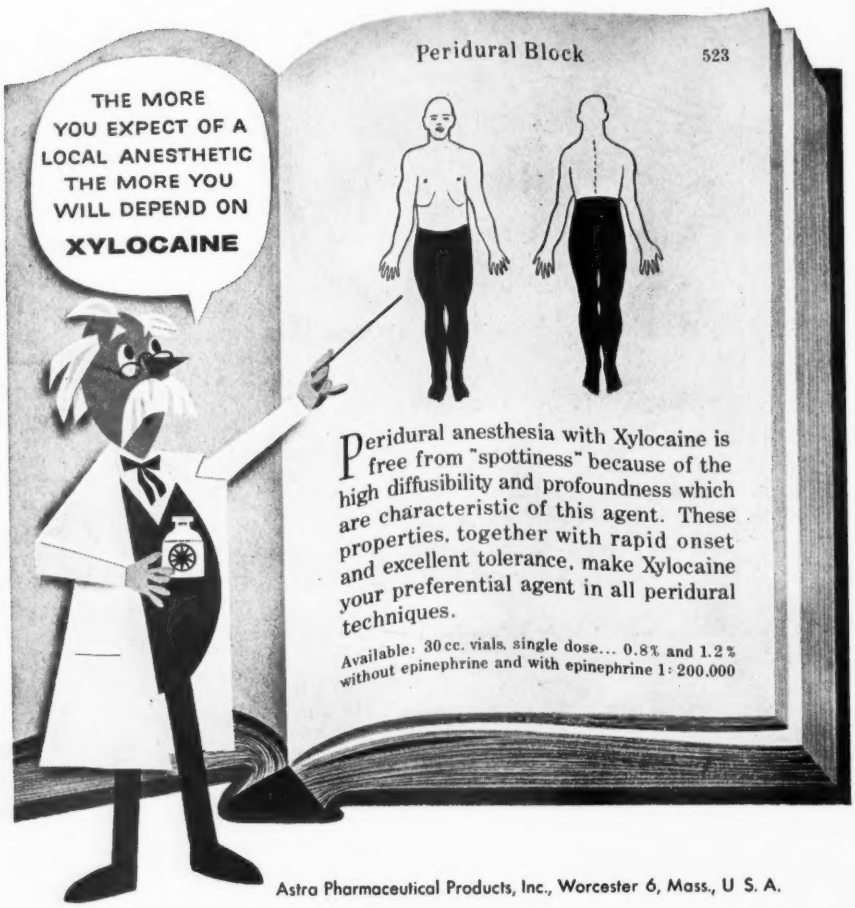
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(brand of lidocaine*)

Sterile solution for injection

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I was putting up my new curtains and draperies last week when . . .

The step-stool wobbled . . . I fell and landed right on my back.

My back and shoulder were so painful — I called my doctor. He gave me a prescription for some tablets and told me to take one right away.

Would you believe it? That tablet worked in 15 minutes! The pain really went away fast — and I got those curtains up without further trouble.

AND THE PAIN WENT AWAY FAST

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Salts of Dihydrohydroxycodeinone and Homatropine, plus APC

FOR PAIN

ACTS FASTER — usually within 5-15 minutes. LASTS LONGER — usually 6 hours or more. MORE THOROUGH RELIEF — permits uninterrupted sleep through the night. RARELY CONSTIPATES — excellent for chronic or bedridden patients. VERSATILE — new "demi" strength permits dosage flexibility to meet each patient's specific needs. PERCODAN-DEMI provides the PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit-forming. Federal law permits oral prescription.

Each PERCODAN* Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. phenacetin, and 32 mg. caffeine.

*U.S. Pat. 2,628,185

Literature? Write

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1. Selzer, A. and Rytand, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 168:762, (Oct. 11) 1958.

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(BRAND OF PIPAMAZINE)

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With its selective action on the vomiting center, or the medullary chemoreceptor "trigger zone," Mornidine possesses the advantages of the phenothiazine drugs without unwanted tranquilizing activity.

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